Central Denmark Region

Outpatient Parenteral Antibiotic Therapy – A Health Technology Assessment

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LIST OF ABBREVIATIONS AND DEFINITIONS

AUH	Aarhus University Hospital
Bronchiectasis	A condition, where the airways of the lungs become abnormally widened, leading to a build-up of excess mucus that can make the lungs more vulnerable to infection
CF	Cystic fibrosis
ECO	Economy
EFF	Clinical effectiveness
ESD	Early supported discharge
EUnetHTA	European Network for Health Technology Assessment
GRADE	Grading of Recommendations, Assessments, Development and Evaluation
HTA	Health Technology Assessment
IPAT	Inpatient Parenteral Antibiotic (Antimicrobial) Therapy
MeSH	Medical Subject Headings
ORG	Organisational
OPAT	Outpatient Parenteral Antibiotic (Antimicrobial) Therapy
PICO	Patient-Intervention-Comparison-Outcome
RCT	Randomised Controlled Trial
RevMan	Review Manager
ROBIS	Risk of Bias in Systematic Reviews
SAF	Safety
SR	Systematic Review
TEC	Technology characteristics

CONCLUSION

In this HTA the preconditions and consequences of using intravenous antibiotic treatment in an outpatient setting or in the patient's immediate environment (OPAT) is described and compared to intravenous antibiotic treatment in the hospital (IPAT). The primary purpose with this project is to assess:

"The extent to which intravenous antibiotic treatment can and should be used in the patients own home in a Danish healthcare setting?".

OPAT has already to a varying extent been used in the Danish regions and municipalities for a number of years and is thus already being used in the Danish healthcare system.

Below the main results of the report are presented with emphasis on the following results:

- The use of OPAT leads to the same or better clinical results as the use of IPAT in included patients with infections and existing evidence shows that OPAT is a safe model for intravenous antibiotic treatment among patients with different infections (quality of evidence: very low)
- The selection of *suitable* patients for the different OPAT models is crucial for a successful treatment. This includes assessment of patientspecific conditions (selfmonitoring and treatment, compliance, patient's understanding of the pros and cons of the technology, etc.)
- The literature indicates that most patients prefer treatment at home compared to hospitalization
- The literature and a microeconomic analysis based on the treatment of various diagnostic cases in a Danish context showed that the OPAT models generally led to a reduction in costs compared with hospitalization in a *socio-economic perspective*.

The literature thus indicates that the current use of OPAT is effective and safe when offered to the right patients and that OPAT has the potential to be cost-saving in a socio-economic perspective.

If the current use of OPAT in the Danish healthcare system is to be increased or developed, a number of factors can be taken into account.

First and foremost, it is important to recognize that OPAT is an extremely complex technology and the possibility to offer OPAT are constantly changing due to new technical solutions, changed pricing, new medicines and organizational changes. The report presents three general models for organizing OPAT, but at the same time describes a number of different more detailed models for OPAT in order to shed light on the many factors that have implications for which models that potentially can be offered in the healthcare system.

There are many viable paths in the further development of OPAT, and appropriate use of OPAT thus involves flexible solutions. The following conditions considered to be important to the further use of OPAT are:

- There is no one-size-fits-all solution, and the choice of OPAT model must be based on careful clinical considerations, taking into account the specific patient's clinical course, needs and resources. Hence, a large differentiated range of OPAT models will increase the likelihood of being able to meet the individual preferences and needs of all eligible patients.
- A large differentiated selection of OPAT models, however, also entails a very large organizational complexity in relation to accommodating the treatment complexity, and the organizational analysis points out that it is challenging to ensure the necessary coordination and communication across municipalities and hospitals.
- If the further development of the use of OPAT is to reduce the organizational complexity, it may be considered to prepare clinical guidelines, including clinical criteria for being offered various OPAT models, which can guide the clinical staff to a more standardized practice based on selected priority OPAT

models. However, this requires a certain standardization of, for example, the use of pumps (elastomeric / electronic) and hospital pharmacies' range of different ready-to-use medicines across the regions.

- The organizational analysis demonstrates the need for education and competence development among especially municipal nurses in Denmark. However, the need for education varies in the individual municipalities and among nurses.
- Finally, the organizational analysis uncover the variation in whether the municipalities currently have the capacity to receive all suitable OPAT patients.
- An increased use of OPAT in a Danish context will thus at present be challenged by the above factors, which is why a decision on further dissemination of OPAT could favourably be focused on a discussion of; 1. possible expansion of capacity in the municipalities, 2. uniform and possibly selected selection of OPAT models followed by established clinical criteria to ensure standardized practice and 3. organizational options that can handle complexity and ensure necessary coordination and communication across municipalities and hospitals.
- As OPAT is a technology in continuous development, it will also be important to discuss how new developments and opportunities are assessed prior to possible implementation and how these are disseminated nationally in an appropriate manner.

1 SCOPE

In this HTA, Outpatient Parenteral Antibiotic Therapy (OPAT) are examined and compared to conventional Inpatient Parenteral Antibiotic Therapy (IPAT) in the hospital. The HTA has been produced at the request of the Health Directors in the five Danish Regions, who found it highly relevant to discover the preconditions for and consequences of using OPAT compared to IPAT, using a HTA approach (Health Director meeting, January, 2020). The purpose of the project is to establish a basis for decision-making prior to prioritization of any further investments/organizational changes concerning integration of OPAT as an alternative to in-hospital treatment. Investigating the area of OPAT potentially includes studying many different patient groups, diverse interventions, varying settings, medical devices, and a wide variety of efficacy measures. Within the given framework of this report defined by regional, clinical and other stakeholders, we will focus into topics of most relevance to the five regions, knowing there will be areas that cannot be fully covered, due to the complexity of the intervention.

Description	Project scope
Population	• In this project all types of patient groups and indications, where OPAT can be of use will be included. For example patients with neutropenia, diverticulitis or exacerbations are included.
Intervention	• "Outpatient Parenteral Antibiotic Therapy" (OPAT) with/without help from another person (primarily healthcare professionals, but also relatives). All kinds of antibiotics, equipment, pumps, organizational (outpatient) settings are included in this HTA (elaborated in Domain 7, ORG)
Comparison	• Conventional Therapy in the hospital that is Inpatient Parenteral Antibiotic Therapy (IPAT), where patients are admitted to the hospital including one or more overnight stay(s). Hence IPAT does not include outpatient treatment (elaborated in Domain 7, ORG)
Outcomes	• Relevant outcomes include e.g. mortality, morbidity, readmissions.
Study design	• For the domains clinical effectiveness (EFF), safety (SAF) and economy (ECO) the following study types will be eligible for inclusion: ○ High quality systematic reviews or meta-analyses of randomized controlled trials (RCTs) or controlled trials/observational studies published within the last ten years and RCTs or controlled trials published within the last ten years. • The domain Patient & Social (SOC) will include quantitative as well as qualitative controlled/non-controlled studies and studies using an exploratory design. • For the description and technical characteristics of technology (TEC) and the organisational (ORG) domains information will primarily be obtained from clinical experts using the technology, and from literature (i.e. descriptive publications) and grey literature as well as anecdotal information from general web-searches.

2 METHODS AND EVIDENCE INCLUDED

2.1 Source of assessment elements

The selection of assessment elements (questions of analysis) was based on the HTA Core Model® (1) . The assessment elements were translated into research questions for each domain/section that would be addressed in this Health Technology Assessment regarding technical characteristics (TEC), clinical effectiveness (EFF) and safety (SAF), patient & social (SOC), organisation (ORG) and economy (ECO). The research questions are formulated on the basis of the generic domain issues from the domains (see HTA Core Model) and can be found under the individual Domains in this report.

2.2 Search

A comprehensive systematic literature search was performed for all domains in the report (Figure 1). The search was performed to meet inclusion and exclusion criteria described in the Scope of this assessment and also addressed the patient, organizational and economy domains. The search was structured via the Patient-Intervention-Comparison-Outcome (PICO) structure. Since this HTA addresses all relevant patient groups, only search terms in relation to the intervention was used in order to uncover all relevant material – thereby not limiting the search by patient, comparator and outcome search terms in order to achieve high sensitivity (and thus low precision) in the initial search. Also this initial search was limited by language (Danish, English, Norwegian, Swedish and German language) and a time limit of 10 years (February 2010 to February 2020).

The search generated 6,378 records, which was reduced to 3,069 studies after removal of duplicates. The search strategy can be obtained from the study authors (example: see Appendix 1 for pubmed search terms).

The following databases were used in the search of studies and guidelines:

- The Cochrane Library (including The Cochrane Database of Systematic Reviews (CDSR), The Database of Reviews of Effects (DARE), The Cochrane Central Register of Controlled Trials, and The Cochrane Methodology Register)
- SCOPUS
- EMBASE
- PubMed
- Psycinfo
- Dissertations & Theses
- Web of Science
- ProQuest Dissertations & Theses Global
- CRD-INAHTA database
- G-I-N
- NICE
- SBU
- Manual search (in reference lists of relevant studies)

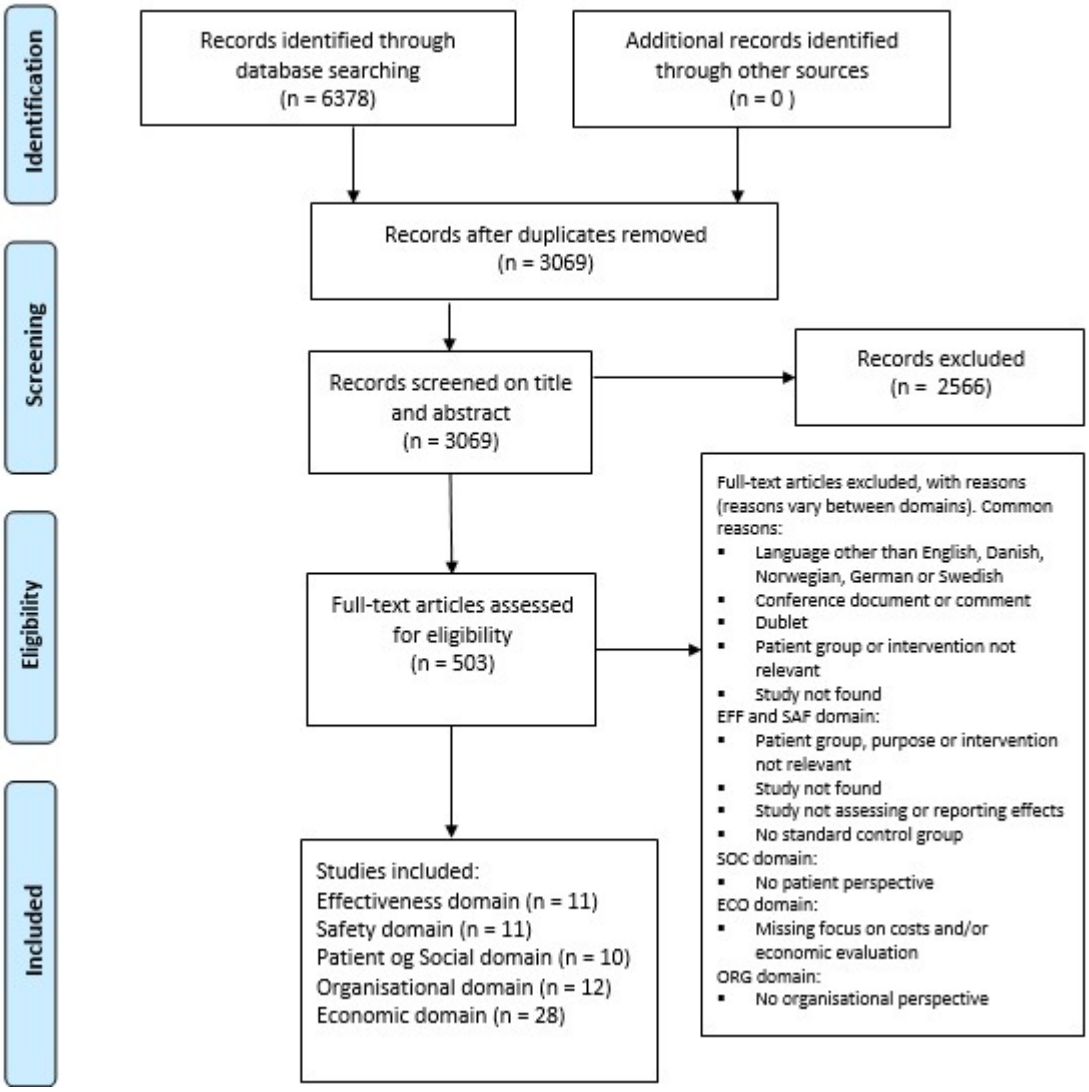
Furthermore clinical trial databases were searched to identify on-going studies on Outpatient Parenteral Antibiotic Therapy (OPAT):

- ClinicalTrials.gov

Beside the systematic literature search, information was sought through clinical and technical experts and internet searches on the topic.

After removal of duplicates, a first selection of studies was done on the basis of title and abstract. Further literature selection was performed independently by two researchers from DEFACTUM using the inclusion and exclusion criteria and according to the research question and PICO scheme. Disagreements were resolved by consensus. The PRISMA flow diagram (Figure 1) displays the phases of literature selection.

Figure 1: PRISMA flow chart of initial study selection



2.3 Study selection

Of the 3,069 studies after removal of duplicates, 2566 were excluded by title and abstract to identify potentially relevant studies, resulting in a parent pool of 503 studies after an overall initial exclusion and selection applying to all domains. From this pool studies for the single domains were selected.

2.4 Data extraction and analyses

Data extraction tables for the domains are shown in each Domain or in the Appendix.

Quality assessment was performed independently by two DEFACTUM researchers for studies included in each domain. Any disagreement was resolved by consensus. For the TEC domain, no quality assessment was applied, but multiple sources were used to validate potentially biased sources. Descriptive analyses of different information sources were applied.

Methods and checklists for quality rating of included studies are described under each domain.

Further methodological descriptions of primary data collection for the domains ‘organisation’ (ORG) and ‘costs and economic evaluation’ (ECO) can be found in these Domains.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
[B0001]	What is Outpatient Parenteral Antibiotic Therapy (OPAT), and what is the comparator Inpatient Parenteral Antibiotic Therapy (IPAT)?
[B0002]	What is the patient characteristics and selection for OPAT compared with IPAT?
[B0003]	What is the route of administration for OPAT compared with IPAT?

In this domain the technology under assessment, 'Outpatient Parenteral Antibiotic Therapy' and its technical characteristics are described as well as its comparator 'Inpatient Parenteral Antibiotic Therapy'. The purpose of the description is to give an overview of the main characteristics as well as differences between diverse ways of delivering intravenous (parenteral) antibiotic therapy in order to differentiate the technology from

its comparator. Detailed descriptions of the technology and its use and the patient group, as well as more in-depth clinical and professional considerations must be found elsewhere. Oral therapy is not a part of this assessment since it is generally used for less severe conditions.

Information in this domain will primarily be obtained from clinical experts using the technology, and from literature (i.e. descriptive publications) and grey literature as well as anecdotal information from general web-searches. In contrast to the other domains, a systematic literature review is not carried out in this Domain and no quality assessment of the literature is applied, although multiple sources are used to validate potentially biased sources.

3.2 Results

The research questions for this assessment refers to *two types* of technologies (including subtypes) when delivering parenteral antibiotic therapy with various infectious conditions. These are: Outpatient Parenteral Antibiotic Therapy (OPAT) and Inpatient Parenteral Antibiotic Therapy (IPAT) as the comparator. Across the literature and document review as well as the interview study in the Organisational Domain 7, it appears that there are several models for the delivery of OPAT.

In broad terms OPAT refers to outpatient management of an infection via the administration of an intravenous (IV) antibiotic medicine without an overnight hospital stay – e.g. at home or as an outpatient, and IPAT refers to inpatient management of an infection via the administration of an IV antibiotic with one or more overnight hospital stay(s). OPAT and IPAT are described in more details below.

Features of the technology and the comparator

[B0001]	What is outpatient antibiotic treatment (OPAT), and what is the comparator IPAT?

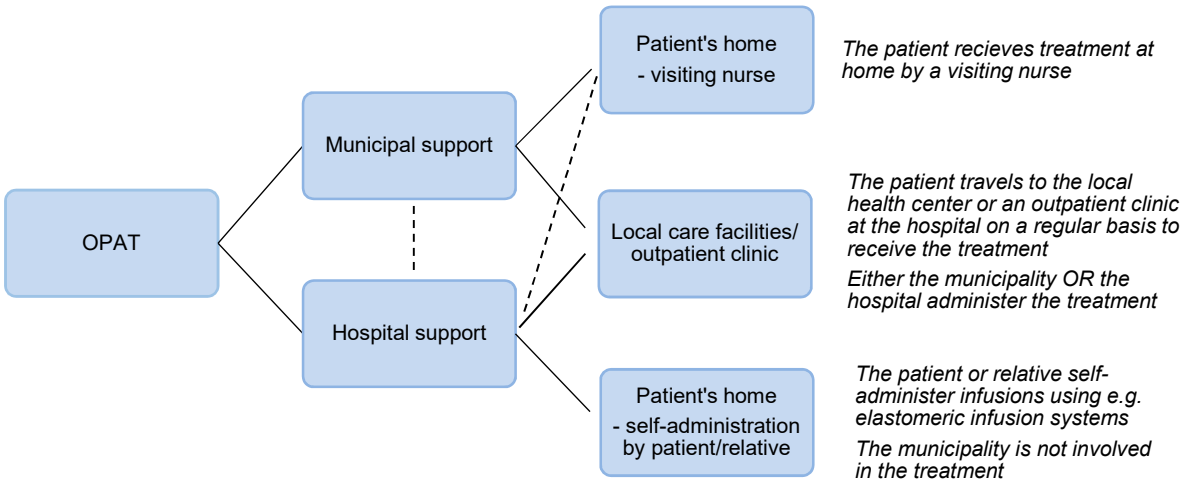
Deciding on the delivery of antibiotic medicine to a specific patient is a complex clinical situation, in which clinicians include information about e.g. patient characteristics, severity and type of condition and technical

opportunities (medicine, pumps, route of administration). Furthermore, clinicians must decide on model of delivery and in this process thus relate to the patient's physical, mental and social conditions as well as the extent to which organizational preconditions enables discharging the patient to some kind of outpatient treatment. At first these OPAT delivery models are described followed by a short description of IPAT.

OPAT delivery models

In general, three delivery models for OPAT in a Danish context are identified. Each model defines the type of administration and arena for the treatment: 1) home administration by a visiting nurse, 2) local care facilities/outpatient clinic or 3) self-administration (Figure 2).

Figure 2: OPAT delivery models in a Danish context



It is important to note that local availability and application of the different OPAT models varies in the five regions. In addition the choice of model as mentioned largely depends on the patient's condition and geographical distance to the hospital (outpatient clinic).

Some of the OPAT delivery models that are widely disseminated in Denmark are also commonly implemented in other Western countries. The three most common OPAT delivery models (figure 2), include home-administration, infusion center administration and self-administration by patient or caregiver. The organisation of these three OPAT models vary locally. Home-administration is either delivered by the hospital ("hospital at home"), the community, or a private health provider. Infusion center administration is delivered in a hospital or a community setting. Additionally, OPAT can be delivered in a specialist parenteral antibiotic therapy clinic within the hospital, in which an OPAT team operates (2-7). Thus, to some extent, the OPAT delivery models implemented internationally correspond to the Danish models (3, 5-7). However – despite a few exceptions – the interview study (see domain 7, ORG) shows that neither *home-administration* by the hospital (hospital at home) or an OPAT team nor *administration in a specialist parenteral antibiotic clinic* managed by an OPAT team is utilized in a Danish context. Furthermore, as opposed to the Danish models, patient or caregiver self-administration is widely disseminated and applied in an international context (2, 4, 7).

If the municipality is involved in the delivery of OPAT, each municipality decides how OPAT is administrated locally. It is among other things determined by the organisation of care in the municipality, local guidelines, eligible patients available, capacity and resources available both in the municipality but also in hospitals referring patients to the municipality. If a patient for example requires parenteral antibiotic treatment four times a day at home, it is not guaranteed that the municipality has the sufficient resources to administer the treatment. This is described in some of the local and regional guidelines. Other municipalities decide whether they will receive the OPAT patient based on the duration of treatment; some municipalities primarily accept short OPAT programs, while others primarily accept long OPAT programs. Also it varies whether the municipal home care service or the municipal acute unit is responsible for OPAT. Medical responsibility for the patient always lies within the referring hospital department.

In those cases, where municipalities manage OPAT, they have the possibility of receiving counselling and feedback from the hospitals. At some hospitals, support units such as outgoing teams or outpatient clinics, that provide support to both hospital departments and municipalities, are established. One example is an OPAT-model tested at the Department of Infectious Diseases at Aarhus University Hospital, that combines telemedicine and user involvement. Here patients are instructed to manage their antibiotic treatment in their own home qualifying them to manage their treatment, without the support of a home nurse. Another example is 'Fælles Daghospital' (FDH) at Odense University Hospital (OUH), which is a daytime hospital firmly anchored in the Department of Rheumatology and primarily staffed by nurses. FDH provides all hospital departments at OUH with technical support in IV treatment and electronic pumps. In FDH, patients receive IV treatment, however, the medical responsibility for the patient still lies within the referring hospital department. Also, at some hospital departments, the organisation encourages regional nurses and physicians to initiate and manage treatment of OPAT patients in the patients home, e.g. the geriatric ward at Aarhus University Hospital.

IPAT

IPAT refers to inpatient management (in the hospital) of an infection via the administration of an IV antibiotic with one or more overnight hospital stay(s). In the hospital setting the antibiotic treatment is the same, but the route of administration may differ in relation to OPAT. In the IPAT setting, the patient receives treatment by the hospital nurses. The main difference in relation to OPAT is obviously, the direct and rapid access to competent clinical staff to deal with possible challenges and complications associated with IV treatment and the clinical condition.

[B0002]	What is the patient characteristics and selection for OPAT compared with IPAT?

OPAT may be deployed within a variety of patient populations in Denmark, and the selection of patients with infection, who are suitable for OPAT is essential in order to achieve appropriate treatment results. The most frequent infections treated with OPAT regimes include lung infections, urinary tract infections, stable endocarditis patients, neuroborreliosis, osteoarticular infections, infections at surgical sites including prosthesis infections, infections with multidrug resistant bacteria, and skin and soft-tissue infections.[2] In some circumstances, IPAT is the only safe treatment option. This applies for example in patients with severe acute infections and those, who require close monitoring or adjunctive therapies (i.e., oxygen, frequent blood testing, bolus intravenous fluid therapy, surgical intervention), though some hospitals are able to maintain close telemedical monitoring and support in the home (8). These patient groups are not good candidates for OPAT and are best managed in an inpatient setting. Frequently, however, the choice between the alternatives IPAT and OPAT is present, and clinicians must decide on the most viable and efficient treatment model. The careful selection of

patients for OPAT or IPAT should include several considerations including severity of the condition, patient mobility, stability of any comorbidity, family and self-care capacities, patient consent, adherence to treatment, shelf life of the medicinal products and venous access for successful outcomes (see domain 7, ORG). As such, it is not possible to set precise criteria for one model instead of the other, since, for example, the patient's medical conditions may suggest OPAT, while the patient's social conditions suggest an IPAT model. Thus, it is mainly a clinical matter, whether the patient accesses OPAT or IPAT.

[B0003]	What is the route of administration for OPAT compared with IPAT?

This section presents an overview in relation to the administration of antibiotics; catheters and administration devices. Types of antibiotics are not mentioned.

Catheters

Intravenous (IV) catheters are an essential part in the process of IV antibiotic treatment of the patients in a hospital as well as out of hospital settings. The choice of suitable *vascular access devices* (VAD) is depending on several factors including age, cognitive status, patient wish, the duration of OPAT, and patient-related conditions such as vascular status, acute/chronic disease, risk of bloodstream infections and thrombosis. Some catheters are administered exclusively for home treatment while other catheters have been placed for other treatment, but can be used for home treatment as well. Catheters that can be used in administration of antibiotic medicine are:

Peripheral venous catheter (PVC)

A peripheral venous catheter is the most commonly used vascular access for both IPAT and OPAT and is usually placed in a vein on the hand or arm. The catheter is introduced into the vein. The catheter is fixed by taping it to the patient's skin or using an adhesive dressing. Very few serious complications are seen, but frequent non-serious complications occur and include infection, phlebitis, extravasation, infiltration, hemorrhage (bleeding), pressure ulcer and formation of a hematoma (bruise)(9).

Midline

Another peripherally inserted catheter is the midline which by definition is 7.5 to 20 centimeters long (3-8 inches) and thus not a central venous catheter. It is inserted in the same peripherally veins as the PICC (see below), but the tip is advanced no further than the distal axillary vein and is therefore classified as a peripheral intravenous catheter with corresponding advantages and disadvantages. Severe complications to placement and use of midline is rare, but due to previous problems primarily related to the midline catheter material, its use has formerly been limited (10).

Central venous catheter (CVC)

Central venous catheters (CVCs) are commonly used vascular accesses in IPAT, but can also be used for OPAT. They are placed via the bigger central vessels often the subclavian or jugular veins. The tip of the catheter is placed in vena cava superior or more centrally. If a longer treatment period is expected, a tunneled CVC can be used. A tunneled CVC is placed in a subcutaneous tunnel before entering into the vein away from the primary skin perforation point to reduce the risk of blood stream infection (11).

Peripherally inserted central catheter (PICC)

Peripherally inserted central catheter (PICC) is a CVC. It is a well-established alternative to CVCs placed via for example the subclavian or jugular veins. PICC is inserted via a peripheral vein in the upper arm and terminates like other central lines in the vena cava superior or more centrally. Placement and use is associated with same complications as CVC (12).

Vascular access port (VAP)

A port is a small medical appliance that is installed beneath the skin. A catheter connects the port to a central vein. Under the skin, the port has a septum (a silicone membrane) through which drugs can be injected. The port is usually inserted in the upper chest where the catheter is inserted into the jugular vein. To get access the skin has to be punctured every time it is used (13).

Application profile

The various available catheters have different applications and safety profiles, and again an individualized treatment strategy of the specific patient is needed. CVC catheters and some PICC/Midline catheters will require children to be sedated, when inserted. In an OPAT setting a general description of available catheters and their application profile is listed in Table 1 below.

Table 1: General description of intravenous catheters used in an OPAT setting

	Expected dwell time (days) before removal/ replacement	***Use – place of insertion***	***Strengths****	***Weaknesses****	***Serious complications****
PVC[1]	*1 - individual clinical assessment*	*Peripheral*	*Easy to place and remove* *Few serious complications*	*Short dwell time* *Discomfort due to frequent replacements* *Frequent non-serious complications* *Unsuitable for longer treatment time* *Risk of extravasation*	*Few*
Midline[4]	*5-28*	*Peripheral*	*Easy to place and remove*	*Frequent non-serious complications*	*Risk of deep vein thrombosis (DVT)*
CVC (tunneled)[2]	*5-14 (14-30)*	*Central*	*Suitable for longer treatment time* *Low risk of extravasation*	*Frequent placements destroy the central vessels* *Difficult to place and remove* *Requires much supervision*	*Few catheter-related bloodstream infections (CRBSI)(tunnelled CVC)* *Risk of DVT*
PICC[3]	*5-90*	*Central*	*Easy to place and remove* *Suitable for longer treatment time*	*Risk of DVT*	*Few CRBSI* *Risk of DVT*
VAP[5]	*> 90*	*Central*	*Suitable for longer treatment time with intermittent use*	*Difficult to place and remove*	*Few CRBSI* *Risk of subcutaneous pocket infection*

** These are some key elements stated in relation to use of catheters.*

[1]Soifer et al., 1998 (9), [2]Xiaoli et al., 2012 (11), [3]Chopra et al., 2012 (12), [4]Anderson et al., 2004 (10), [5]Walser, 2012 (13).

Medicine and administration devices

Administering antibiotics outside the hospital requires a set-up that reflects the conditions in the hospital. This includes competent handling of utensils and medicine, hygienic arrangements and a stable environment in relation to administration. As a special focus in OPAT, safe handling of the antibiotics to protect both patient, staff and environment is required. Sterility off the product as well as infusion sets/utensils must be maintained and the escape of aerosol or droplets from the antibiotics into the surrounding environment must be prohibited. This means that preparation and administration of the drug must take place using a closed system. The closed systems used in OPAT are typically ready to use drugs, but also includes special infusion sets that allow the preparation of the drug to take place under controlled conditions (14). Choice of systems/procedure depends for example on type of medication, shelf life and dosage.

Continuous Ambulatory Delivery Device (CADD)

The CADD pump is a small battery powered infusion pump. This infusion pump delievers IV medication at a controlled dose and rate to the patient. The pump contains a cassette with the antibiotic medicine and is a little bigger and heavier than a smartphone. The medicine is connected to tubing and is given through the IV catheter. This delivery method allows for the correct dose of antibiotics to be administered correctly (https://www.smiths-medical.com/brands/cadd).

Examples of ready-to use drug systems:

Duplex

A dual chamber IV container that stores the drug and diluent in separate compartments until the seal is broken just prior to administration (15)

Elastomeric Pumps

Elastomeric Pumps are non-electronic medication pumps designed to provide continuous infusion of the medication. Medication is delivered to the patient as the elastomeric “balloon” consistently deflates and gently pushes solution through the IV tubing and into the catheter(16).

Prefilled bags and syringes

Prefilled and mixed bags and syringes are ready for infusion of the medication. The medication can be given as a bolus or mounted on an electrical pump and given as a continuous or intermittent infusion through hours and days.

Divibax

A medicine mixing system consisting of a connector that links the drug vial and the IV container. The drug and diluent is stored in separate compartments, until the system is "activated" just prior to administration(17).

This concludes the overview of the predominant aspects of what kind of technology Outpatient Paranteral Antibiotic Treatment is, and how it can be employed in an out of hospital setting. The purpose is to present a brief introduction to the topic in order to get an overall understanding of the use of OPAT in Denmark. The coming domains will provide further insight into effectiveness, safety and consequences for patients, organisation and economy thereby further unfolding the technology and its role as an alternative to Inpatient Parenteral Antibiotic Treatment.

4 CLINICAL EFFECTIVENESS (EFF)

4.1 Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of Outpatient Parenteral Antibiotic Therapy (OPAT) on mortality in relation to Inpatient Parenteral Antibiotic Therapy (IPAT)?
D0005	How does use of OPAT affect symptoms and findings (severity, frequency) of the patients undergoing antibiotic therapy?
D0006	How does OPAT affect progression (or recurrence) of the infection/ health condition?
D0012	What is the effect of OPAT on generic and disease-specific health-related quality of life?
D0017	Were patients satisfied with the use of OPAT?

Outpatient Parenteral Antibiotic Therapy (OPAT) is an opportunity for patients, previously hospitalized (IPAT), to receive treatment in their own home, in an acute or temporary institution or e.g. a nursing home, and self-administration of antibiotics using pumps has become more and more frequent over the years. OPAT is compared to IPAT and separate analysis is made for OPAT in an ambulant setting (local care facility) compared to relevant alternatives. Desired and expected clinical effects are manifold e.g. reduced number of readmission and increased satisfaction with treatment.

4.2 Methods

A comprehensive literature search has been conducted (section 2.2.), which for the EFF domain resulted in 11 included studies (Figure 3). In addition to the aforementioned selection criteria (see Scope) the following study types were eligible for inclusion: High-quality SRs or meta-analyses of RCTs or controlled trials, RCTs or prospective controlled trials.

Studies that compared different types of medicine or equipment were excluded. Studies that compared IV vs. oral treatment in an outpatient setting were also excluded.

Data extraction and analyses

Data from the included studies were extracted using a standardised data extraction form. Data extraction was performed independently by two DEFACTUM researchers.

Quality rating

The quality of included reviews was assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool. RCT studies were assessed using the Cochrane risk-of-bias tool. Risk of bias in cohort studies were assessed using Scottish Intercollegiate Guidelines Network (SIGN) methodology checklists. The quality of the body of evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE). For relevant outcomes, an evidence profile was generated using the GRADEpro software. Results are presented narratively. Statistical summary estimates of associations across studies will if possible be derived using random effects meta-analysis, anticipating clinical heterogeneity and with modelling allowing for differences in associations from study to study. Heterogeneity across studies will statistically be assessed using the Q-test and quantified by the inconsistency (I^2) index, where I^2 represents the percentage of total variation across

studies attributable to heterogeneity rather than (statistical) chance. In cases with substantial heterogeneity across studies (I^2 >50%), the robustness of the results will be checked using a fixed effects model. A result is considered robust, if the point estimate based on the fixed effects analysis is within the confidence interval of the random effects analysis. Meta-analyses will be performed using Review Manager (RevMan, the Cochrane Collaboration). A two-sided p-value of <0.05 is considered to be statistically significant in all analyses.

A considerable diversity in applied outcomes and methods of recording the effects is expected. Within reasonable limits, this is handled, in this HTA, by compiling relevant outcomes for a total inventory despite minor variations in the individual studies (Table 2). This is necessary to ensure adequate data material to analyse, whereas the alternative with many small analyses would have only limited (statistical) value. Thus, a pragmatic approach will be used to ensure generalizability of the outcomes for clinical practice.

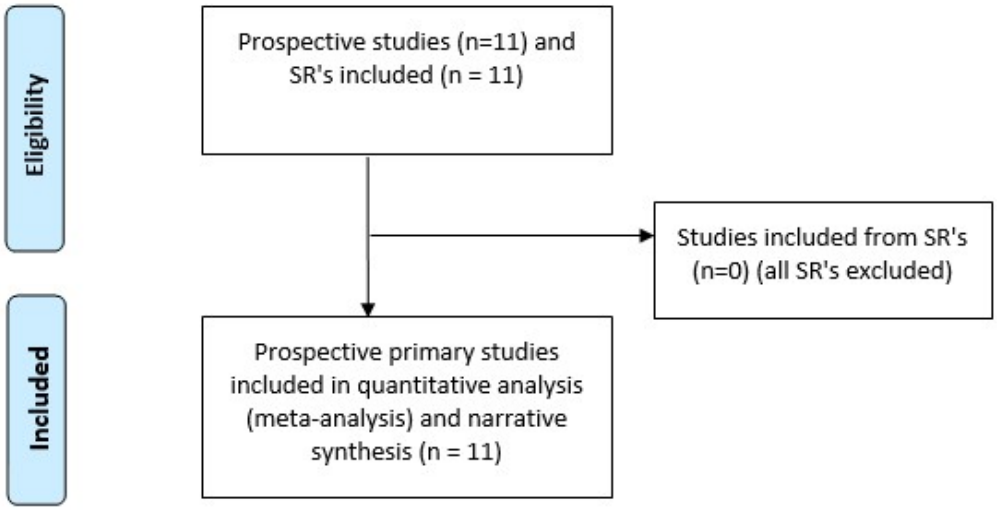
Table 2: Outcomes

Outcome	
▪ Readmission:	Any readmission after discharge. Follow-up are specified in some studies.
▪ Mortality:	Any mortality in outpatient/inpatient groups
▪ Morbidity:	Three morbidity outcomes are reported in this Domain: resolution of infection, lung function and clinical success.
▪ Quality of life	
▪ Satisfaction	

4.3 Results

Literature selection for the EFF domain was performed by full text review by two project participants, resulting in inclusion of 11 primary studies, seven observational studies and four RCT studies. Details of the studies are provided in Table 3. Initially 11 reviews were included from which relevant primary studies from 2010 and forward were to be included (18-28). Eventually though, no studies from reviews were included (Figure 3). Reasons for not including studies from systematic reviews were e.g., that studies were single-cohort studies, no intervention was applied, purpose was not relevant, or that the study was addressing health economy.

Figure 3: Elaboration of the PRISMA flow chart (Figure 1) for included studies in effectiveness domain



The included studies display great variation in types of infections and outcomes (Table 3), as well as discrepancy in delivery of OPAT and settings for the studies. Review of the effect measures also reflects a certain diversity in relation to the definition and procedure for registering the effects. Four studies from USA, four studies from Australia, and one study from respectively UK, Greece and Spain were included. Overall 4221 patients were included representing children, adolescents, adults and elderly.

Table 3: Characteristics of included studies

Study ID Author, year, country	Aim of study Study design/ type	Methods			Results/comments
		Population/patient description/ characteristics	Intervention(s) vs. comparison(s) and description/characteristics	Main outcome(s)	
Hendricks et al. 2011 USA (29)	To assist clinicians and families in decision making by comparing IPAT with OPAT. Multicenter RCT	Oncology patients with cancer chemotherapy-assisted fever and neutropenia (n=92) (mean age: 43-47 years)	OPAT after inpatient observation (with daily nurse home visits) compared with IPAT.	Complications Quality of life	No differences in QOL was found. No differences were found in major medical complication rates (home, 9% vs. hospital, 8%; P=0.56; 95% CI for increased major medical complication rate for the outpatient treatment arm - 10% to 13%).
Rodríguez-Cerrillo et al. 2013 Spain (30)	To compare the outcomes of patients treated at home versus traditional Hospitalization Cohort study	Elderly patients with uncomplicated diverticulitis. (n=52, 34 at home and 18 hospitalized (mean age: 77 and 79 years).	Patients were admitted to Hospital at Home Unit (nurses administrating medicine) or to Conventional hospitalization from the Emergency Department. Mean stay was 9 days in Hospital at Home and 10 days in Hospital.	Clinical evaluation	All patients had a good clinical evolution. None of the patients treated at home were transferred to Hospital
Bedi et al. 2014 UK (31)	To assess the efficacy and safety of OPAT compared with IPAT Cohort study	Patients with non-cystic fibrosis bronchiectasis with acute exacerbation (n=116) (mean age: 61-71 years)	IPAT compared with early discharge supported group (EDS) and OPAT group, hospital and domiciliary setting, All patients received 14 days of IV antibiotic therapy. OPAT-patients were taught to self-administer IV antibiotics.	Clinical and QOL Morbidity Mortality 30-day readmission rates	Clinical and QOL improvement in all groups, with resolution of infection in 76% in the IPAT, 80% in the ESD group and 80% in the OPAT group. Morbidity was recorded in 13.8% in the IPAT, 9.4% in the ESD group and 14.2% in the OPAT group. No mortality was recorded. Thirty-day readmission rates were 13.8% in the IPAT group, 12.5% in the ESD group and 14.2% in the OPAT group. Total bed days saved were 1443.
Orme et al. 2014 Australia (32)	To compare quality of life (QOL) between inpatient and outpatient intravenous antibiotic management. RCT	Children and adolescents receiving low/moderate intensity chemotherapy with low risk febrile neutropenia (LRFN) (n=27, 37 presentations). Age: 1-21 years.	Eligible participants were randomised to outpatient versus inpatient treatment. Outpatients were observed in the ED for a minimum of 4 hours. After discharge, Home and Community Care (HACC) nurses visited twice daily. Patients randomised to the inpatient arm received routine inpatient monitoring and care. Antibiotic therapy was continued in all patients for a minimum of 48 hours, until resolution of fever for 24 hours	Quality of life (QOL) was measured during the enrolment episode. At baseline, and daily for each day of cefipime treatment, until fever and neutropenia resolved or readmission of outpatients Occurred. Adverse events prospectively	Absolute scores not presented. No differences in QOL between patient groups. Some differences in QOL between parent-groups.
Chrysochoou et al. 2016 Greece (33)	To compare safety, efficacy and cost benefits of OPAT versus IPAT. Cohort study.	Children and adolescents with stable cystic fibrosis (CF) colonized with Pseudomonas aeruginosa (mean	IPAT group compared with OPAT group, treated with IV antibiotics for two weeks either in hospital or at home supervised by a nurse weekly.	Clinical outcomes QOL Complications	IPAT did not show a better clinical outcome compared with OPAT. Lung function and weight improved significantly in both groups (ΔFEV1, p =0.606, ΔWeight, p =0.608). Significant differences in QOL scores between the groups in favour of OPAT (mean: 3.6 (p=0.04))

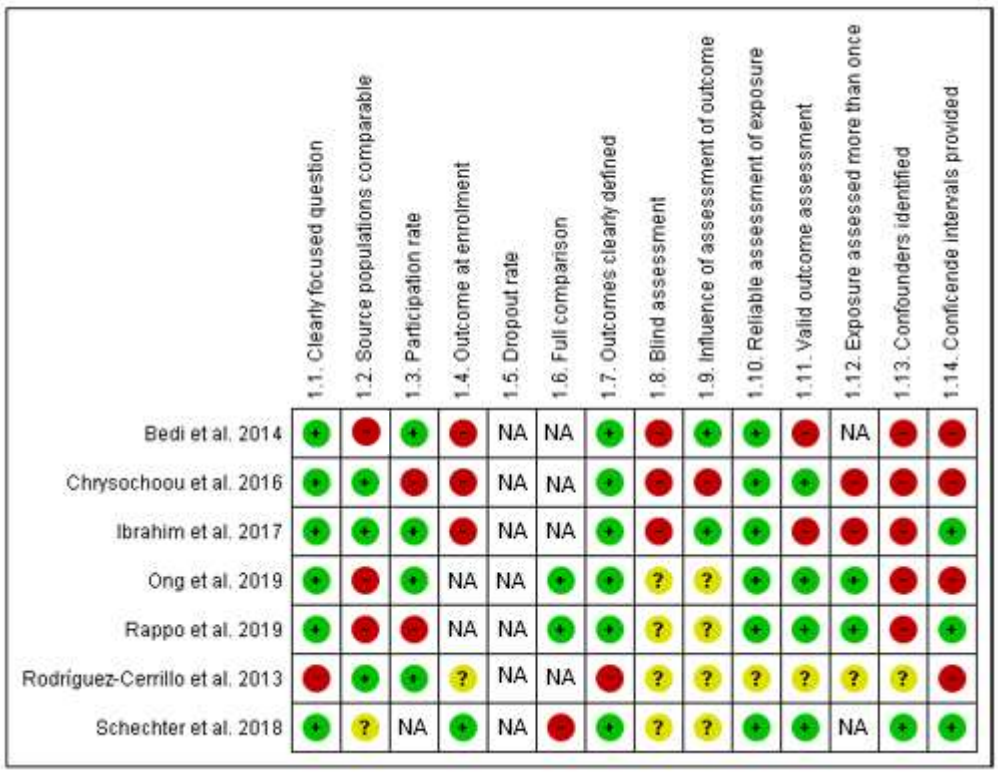
		age: 12.6 ± 7 years) (n=35)	Two nurses trained the children and their parents how to administer IV antibiotics,		No complications in the OPAT group.
Ibrahim et al. 2017 Australia (34)	To evaluate the outcomes for OPAT compared with IPAT. Cohort study.	Children with moderate to severe cellulitis 6 months to 18 years (n=115), from March 2014 to January 2015.	OPAT in the home from the Emergency Department (nurse administering medicine on a daily basis) compared with IPAT. Duration of intravenous antibiotics (median 1.9 vs 1.8 days, OPAT vs IPAT respectively)	Treatment failure Duration of IV antibiotics Complications Treatment costs	2/47 (4%) in the OPAT group compared with 8/59 (14%) in the IPAT group had treatment failure (P=0.10). Duration of intravenous antibiotics (median 1.9 vs 1.8 days, P=0.31) and complications (6% vs 10%, P=0.49) were not different between groups. Complications during treatment were few in both groups and not different between groups.
Schechter et al. 2018 USA (35)	To compare inpatient treatment with outpatient treatment. Cohort study	Patients 6 years of age or older with acute pulmonary exacerbations in cystic fibrosis	For each treatment site time in inpatient care and outpatient care is estimated. The median total number of days of treatment was 14.	Primary definition of treatment response: return of ppFEV1 to greater than or equal to 90% of baseline within 30 days after treatment end.	The primary model revealed an absolute increase of 9.08% (95% confidence interval, 2.55–15.61; P = 0.006) in the achievement of a return of percent predicted forced expiratory volume in 1 second to greater than or equal to 90% of baseline comparing complete inpatient treatment with no inpatient treatment.
Ibrahim et al. 2019, Australia (36)	To compare the efficacy and safety of OPAT with IPAT. RCT.	Children with moderate to severe cellulitis, (n=190)	IPAT with intravenous flucloxacillin or OPAT with intravenous ceftriaxone (the homecare team were available 24 h a day, 7 days a week. The nurse administering medicine on a daily basis). Duration of intravenous antibiotics (median 2.2 vs 1.7 days, OPAT vs IPAT respectively)	Treatment failure Adverse events Acquisition of antibiotic-resistant bacteria	Treatment failure occurred in two (2%) children in OPAT group and in seven (7%) children in the IPAT group (risk difference –5·2%, 95% CI –11·3 to 0·8,p=0·088). Fewer children treated with OPAT had an adverse event (two [2%] vs ten [11%]; p=0·048). There was no difference between groups in rates of nasal acquisition of meticillin-resistance.
Ong et al. 2019 Australia (37)	To review Hospital in the Home (HITH) program compared to patients, who are admitted to hospital. Cohort study	Patients aged 18 years and above with a clinical diagnosis of cellulitis (n=100)(38% women). Mean age HITH: 57, hospital: 69	HITH vs. hospital Patients were classified as HITH, if they were directly admitted to HITH or continued treatment via HITH after hospital admission. The two cohorts were: patients who were entirely treated in hospital, and those who were treated partially or entirely in the Ambulatory Care HITH program (home visits up to twice a day). Duration of intravenous antibiotics (median 7.0 vs 5.7 days, OPAT vs IPAT respectively)	Clinical recurrence, hospital readmission and mortality. Patients were followed up for 28 days following completion of intravenous antibiotics.	Patients treated in hospital had a higher incidence of acute renal failure (27.1% vs 3.8%, p=0.001), nosocomial infection (10.4% vs 0.0%, P=0.023), and a higher 28-day hospital readmission rate (10.4% vs 0.0%, P=0.023).
Rappo et al. 2019 USA (38)	To assess the efficacy, safety and patient satisfaction of Dalbavancin in the outpatient and inpatient setting. Cohortstudy in relation til setting (RCT in relation to antibiotics)	Patients with acute bacterial skin and skin structure infections (ABSSSI)(n=698, 386 outpatients (mean age 45) and 312 inpatients (mean age 52)).	In a subanalysis patients were followed as a cohort as in-/outpatients. 386 treated as outpatients and 312 as inpatients.	Primary outcome: 20% reduction in erythema. Secondary outcome: clinical success - improvement in lesion size from baseline, and resolution or improvement of clinical	Efficacy outcomes at 48–72 h, Days 14 and 28 were similar between patients treated in the outpatient and inpatient Outpatients reported significantly greater convenience and satisfaction with antibiotic treatment and care setting compared with inpatients (P < 0.001). Clinical success: Calculated RR: 0.98 (0.94-1.03)

				signs and symptoms. Clinical success required 80% reduction in lesion area on Day 14 and 90% reduction on Day 28 Patient satisfaction	
Fanucchi et al. 2020 USA (39)	To evaluate OPAT with IPAT. Pilot RCT	Patients with opioid use disorder (OUD) with severe injection-related infections (SIRI) (18-65 years) (n=23)	OPAT in hospitalized adults with OUD and SIRI compared with IPAT. Treatment period was on average more than 6 weeks.	Clinical and drug use outcomes Hospital stays Complications	OPAT group had similar clinical and drug use outcomes to IPAT group. OPAT group had shortened hospital length of stay compared with the IPAT group by 23.5 days. The average length of hospital stay for OPAT participants was 22.4 (standard deviation [SD] ± 7.1) days compared to 45.9 (SD ± 7.8) for IPAT patients.

The quality of the individual studies are shown in Figure 4 and 5 for observational (cohort studies) and RCT's studies respectively.

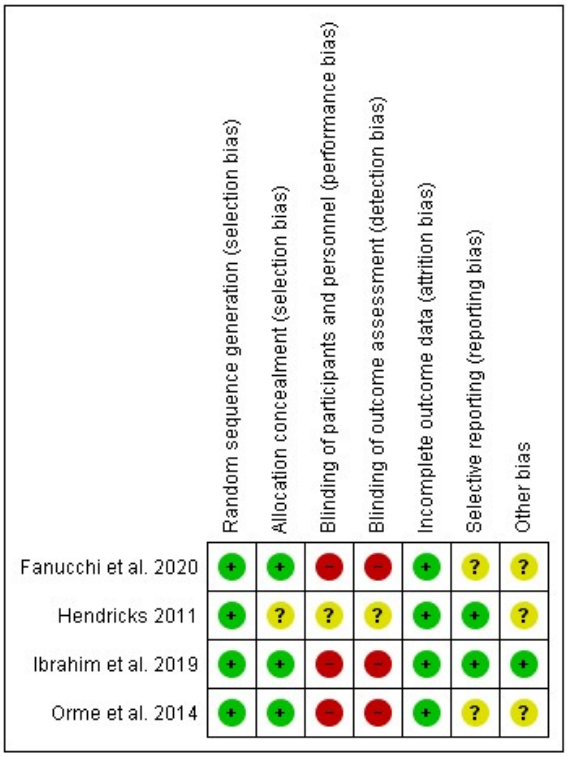
Looking at observational studies, studies were found to be mostly at high or unclear risk for the majority of the 'Risk of bias' domains except for 'clearly focused questions', 'outcomes clearly defined' and 'reliable assessment of exposure'. For RCT studies selection bias and attrition bias were low in risk. Due to the nature of interventions, it is difficult to maintain blinding procedures; participants will know which treatment they receive as will treatment personnel, and some outcome measures will be affected by lack of blinding. Overall bias in the included studies are likely to affect the study estimates and thereby reduce our confidence in the estimates.

Figure 4: Risk of bias in cohort studies



NA: non-appliable

Figure 5: Risk of bias in RCT studies



In the following sections, the results for the selected effect measures are presented. Unfortunately, the great diversity in the study design entails that only one meta-analyses can be implemented and consequently that the majority of results are presented narratively.

Mortality

[D0001]	What is the expected beneficial effect of Outpatient Parenteral Antibiotic Therapy (OPAT) on mortality in relation to Inpatient Parenteral Antibiotic Therapy (IPAT)?

Two studies (one cohort study and one RCT) reported on mortality. In one study including patients with bronchiectasis and diverticulitis, no mortality was recorded among the included patients (31). In another study by Ong et al. two patient deaths were recorded among hospitalized patients. In this study patients admitted to hospital treatment were significantly older, and had more comorbidities and severe illness (37). Thus, no definitive conclusions can be drawn regarding mortality based on included studies. These low quality results do not suggest any difference between patients treated in the hospital or at home.

Morbidity

[D0005]	How does use of OPAT affect symptoms and findings (severity, frequency) of the patients undergoing antibiotic therapy?

The outcome measures are very different in the included studies. In this section 'resolution of infection', 'lung function' and 'clinical success' are reported. The 'safety' domain (Domain 5) reports on 'morbidity rates' which here is to be interpreted as complications and on exerbations in CF-patients.

Resolution of infection:

In one cohort study resolution of infection (potentially pathogenic microorganisms) in patients with bronchiectasis was significantly reduced by 76% in the IPAT and 80% in the OPAT group. (31). No significant difference between the groups from day 1 to day 14 was shown.

Lung function:

In three cohort studies examining patients with bronchiectasis and cystic fibrosis exarbations lung function improved significantly in both inpatients and outpatients (31, 33, 35). Lung function was measured using forced expiratory volume in 1 second, a widely used and validated measure to demonstrate lung function (here as a surrogate measure revealing the underlying condition – lung infection). In the two cohort studies by Bedi et al. and Chryschoou et al. no difference between groups was shown, whereas in the study by Schechter et al. an absolute increase of 9.08% (95% confidence interval, 2.55–15.61; P = 0.006) in the achievement of a return of percent predicted FEV1 comparing inpatient treatment with no inpatient treatment was shown.

Clinical success:

In patients with acute bacterial skin and skin structure infections Rappo et al. studied differences in clinical success between inpatients and outpatients. Clinical success were defined as requiring an 80% reduction in lesion area on Day 14 and a 90% reduction on Day 28. 92% of outpatients (275/300) and 93% inpatients (222/238) achieved clinical success on day 28 (RR=0.98), and thus no difference between groups (38)

Rodríguez-Cerrillo et al. only state in their study, that all patients had a good clinical evolution, and that none of the patients treated at home was transferred to Hospital (30).

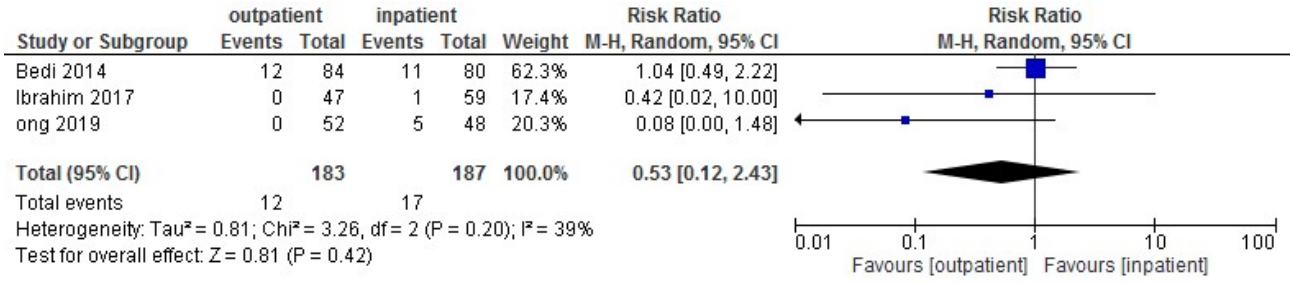
Readmission

[D0006]	How does OPAT affect progression (or recurrence) of the infection/ health condition?

In four studies, one RCT (36) and three cohort studies (31, 34, 37) readmission was measured. 'Length of stay' is reported in the safety domain (39). Main reasons for readmission was recurrence of infection or failure of treatment. Participants investigated were patients with bronchiectasis or cellulitis (children and adults). Follow-up timelimits were specified in two studies as 30 days follow-up and in two studies as any readmission after discharge.

The metaanalysis (Figure 6) revealed a non-significant tendency in favour of patients treated in the home describing a risk ratio of 0.53 for cohort studies (low to moderate heterogeneity, I^2 value of 39%), although the calculated RR for patients in the RCT were 1.02 (CI: 0.15 – 7.10). No studies were in favour of hospitalized patients. Although patient characteristics were not similar in the study by Ong et al., results from these analysis indicate no significant differences in readmissions between the groups.

Figure 6: Metaanalysis readmission



Health-related quality of life

D0012	What is the effect of OPAT on generic and disease-specific health-related quality of life?

Health related quality of life was evaluated in three studies, two RCT's (29, 32) and one cohort study (33). Health related quality of life was measured using a VAS-scale (32), condition-specific cystic fibrosis question-naire (DISABKIDS)(33) and an unspecified scale in the study by Hendricks et al. Due to different ways of measuring quality of life it was not possible to perform a metaanalysis.

Chrysochoou et al. reported a significant difference in cystic fibrosis children in favour of home treatment (diff.: 3.6 (p=0.04)). In two studies by Hendricks et al. and Orme at al. no absolute scores were reported. Both studies found no difference in QOL in febrile neutropenia patients treated at home or in hospital.

Satisfaction

D0017	Were patients satisfied with the use of OPAT?

Only two studies reported on satisfaction (one RCT, one cohort study). In a study of children with cellulitis, parents were asked 7–14 days after discharge to rate their experience on a five-point Likert scale with the

treatment. 69 of 73 parents in the home group rated the experience of care as 'very good' compared with 45 of 62 parents in the hospital group (p=0.0014) (36).

In the other study by Rappo et al. patient satisfaction were measured using the 10-item Skin and Soft Tissue Infection (SSTI) questionnaire at Day 14 (38). In this study patients with acute bacterial skin and skin structure infections were investigated. Patients in the outpatient group reported being ‘very satisfied’ or ‘extremely satisfied’ more often compared with inpatients regarding their antibiotic treatment and the location (i.e. outpatient or inpatient setting) of the care they received (93 % vs. 84 %, P < 0.001).

In the GRADE evidence profile for the outcome measures all estimates are presented along with the certainty of the evidence behind the estimates (Table 4). It is noticed that confidence in the estimates is very limited, and that the estimates might very well change in future studies. Though it is also noticed that differences between the groups are equal or points in the direction in favour of OPAT, which makes us more confident that the clinical effects of using OPAT probably will not be inferior to using IPAT in patients with infections.

Table 4: GRADE evidence profile. Outpatient Parenteral Antibiotic Therapy (OPAT) versus Inpatient Parenteral Antibiotic Therapy (IPAT)

Quality assessment							Effect		Certainty
Outcome (number of studies)	**Study design**	**Risk of bias***	**Inconsistency**	**Indirect evidence**	**Imprecision**	**Publication bias**	**Relative (95 % CI)**	**Absolute**	
Resolution of infection (1)	Observational study	Serious	NA	None	Serious	Not detected		IPAT: 76 % OPAT: 80 %	⊕OOO VERY LOW
Clinical success (1)	Observational study	Serious	NA	None	None	Not detected	RR=0.98 (CI: 0.94-1.03) in favour of IPAT		⊕OOO VERY LOW
Readmission (3)	Observational study	Very serious	Serious	None	Serious	Not detected	RR=0.53 (CI: 0.12 – 2.43) in favour of OPAT		⊕OOO VERY LOW
Readmission (1)	RCT	Serious	NA	None	Very Serious	Not detected	RR=1.02 (CI: 0.15 – 7.10)		⊕OOO VERY LOW
Quality of Life (1)	Observational study	Serious	NA	None	NA	Not detected		Diff.: 3.6 (p=0.04) in favour of OPAT	⊕OOO VERY LOW
Satisfaction (1)	Observational study	Serious	NA	None	NA	Not detected		93 % vs. 84 % (p<0.001) in favour of OPAT	⊕OOO VERY LOW
Satisfaction (1)	RCT	Serious	NA	None	NA	Not detected	RR=1.3 (p=0.0014) in favour of OPAT		⊕OOO VERY LOW

* See Figure 4 and 5.

Mortality is not presented in the GRADE table.

Four of five outcomes only describe results from one study.

NA: not applicaple, not available

4.6 Conclusion

In this report Outpatient Parenteral Antibiotic Therapy (OPAT) refers to administration of antibiotics in an out of hospital setting (cf. domain 3, TEC), but includes ambulant treatment as a separate analysis, which in some

studies are excluded as in-hospital treatment. Some of the main drivers for OPAT are patient welfare, reduction of risk and better or as a minimum same treatment results.

Overall, the certainty of the evidence in relation to the results in this Domain is very low, partly based on the design of the studies (observational studies) and partly on an assessment of the quality. Eleven peer-reviewed RCT and observational studies form the basis of these results. Settings, patient groups and outcome measures are quite different between the included studies, which remain a challenge in relation to transferability of the results. In a Danish context, variation is also a prominent feature of this type of treatment, which further limits the transferebility. Also in three studies comparability between patient groups are limited.

Having said this, it should be noted, that the results provide an important indication as to the clinical effect of applying OPAT among different patient groups, as it refers to its performance under 'real-world' conditions.

In this HTA, results regarding readmission are aggregated despite minor variations in the individual studies. This is necessary to ensure sufficient data material to analyze, whereas the alternative with many small analyzes would have limited (statistical) value. It also reflects the clinical reality, where, depending on the local conditions, there will be variations in, for example, delivery of service, equipment and local regimens. Thus, a pragmatic approach has been used to ensure generalizability of results. Also only prospective randomized and non-randomized studies were included in order to preclude some of the bias inherent in retrospective designs, which is especially prevalent in these types of complex interventions. Likewise it is as a limitation factor mentioned in severel non-randomized studies (31) (33, 37) that allocation is completed on the basis of the patients health condition, which introduces bias to the study – groups are thus less comparable. No Danish studies were included in this HTA. The context for delivering outpatient care are further discussed in Domain 7 'Organisational'.

In relation to 'clinical success', 'readmission' and 'resolution of infection' minor to moderate insignificant differences primarily in favour of OPAT were found. In relation to 'Quality of life' and 'satisfaction' minor to moderate significant differences were found in favour of OPAT. Based on the available evidence no further conclusions regarding specific patient or age groups can be made. No studies reported on separate 'emergency department' groups, although patients in the study by Ong et al. were treated partially or entirely in the Ambulatory Care (37). In most studies, patients were visited on a daily basis for administration purposes or as a control function. Self-administration was only mentioned in two studies (31) (33).

Ideally, as mentioned by Bedi et al. (31) domiciliary treatment should be as effective as inpatient treatment (or better). Although results originate from studies located in different context and settings and across patient groups, results consistently favours OPAT or are equivalent. Other systematic reviews presented similar results, and further concluded that randomised studies of the efficacy of this strategy are needed (18, 19, 22, 24).

5 SAFETY (SAF)

5.1 Research questions

Element ID	Research question
[C0008]	How safe is the use of Outpatient Parenteral Antibiotic Therapy (OPAT) in relation to Inpatient Parenteral Antibiotic Therapy (IPAT)?
[C0002]	Are the harms related to dosage or frequency of applying the technology?
[C0007]	Are the technology and comparator(s) associated with user-dependent harms?
[B0010]	What kind of data/ records and/or registry is needed to monitor the use of the technology and the comparator?

5.2 Results

Included studies

This domain included nine of the 11 included studies from the literature search in the clinical effectiveness (EFF) domain, where quality assessment of these studies are shown (see Domain 4). The included RCT's and observational studies in this domain reported safety concerns using OPAT compared with IPAT for various diagnoses and outcomes in heterogeneous populations.

Patient safety

Element ID	Research question
[C0008]	How safe is the use of Outpatient Parenteral Antibiotic Therapy (OPAT) in relation to Inpatient Parenteral Antibiotic Therapy (IPAT)?

The studies showed, that there are few safety concerns, when using OPAT instead of IPAT as a health-care delivery model in treatment of patients with diagnoses such as non-cystic fibrosis bronchiectasis, uncomplicated moderate to severe cellulitis in children, opioid use disorder with injection-related infections, and acute bacterial skin infections (see Table 5). They found that safety outcomes such as rate of treatment failure (any change of the initial empiric antibiotics within 48 hours due to inadequate clinical improvement), serious adverse events, IV access complications and overall complications (i.e. abscess or rash) were low with no overall difference between the groups. However, a few of the studies (36, 37, 40) indicated a significantly lower frequency of length of stay, treatment time, treatment failure, acute renal failure and lower incidence of nosocomial infections in the OPAT group compared with the IPAT group.

Table 5: Results from the included studies on safety

Author	Results
Bedi et al. (31) 2014 *Cohort study*	No IV access related complications (including line sepsis, line blockage, line fell out) in the IPAT group in comparison to 6.3% in the Early Supported discharge (ESD) group and 3.6% in the OPAT group.
Orme et al. (32) 2014 RCT	In pediatric oncology patients with low risk febrile neutropenia, there were no serious adverse events attributable to OPAT compared with IPAT. The mean length of treatment days and fever was equivalent between the groups (p=0.12).
Chrysochoou et al. *(33)* *2016* *Cohort study*	In children and adolescents with cystic fibrosis colonized with Pseudomonas aeruginosa, there were no complications in the OPAT group compared with the IPAT group.
Ibrahim et al. (34) 2017 *Cohort study*	In children with uncomplicated moderate to severe cellulitis, (4%) in the OPAT group compared with (14%) in the IPAT group had treatment failure (P=0.10). Complications (development of abscess and rash) were 6% in the OPAT group vs 10% in the IPAT group, (P=0.49). Duration of IV antibiotics were comparable between groups, 1.9 days in the OPAT group vs. 1.8 days in the IPAT group, (P=0.31).
Fanucchi et al.(39) 2019 *Pilot RCT*	In patient with opioid use disorder and severe injection-related infections, one catheter-related complication in the IPAT-group was observed and no serious complications in the OPAT group. The average length of treatment for the OPAT patients was 22.4 days compared with 45.9 days for the IPAT group.
Ibrahim et al. (36) 2019a *RCT*	In children with cellulitis, treatment failure (defined as no clinical improvement) occurred in the intention to treat analysis, 2% of the children in the OPAT group and in 7% in the IPAT group (p=0.088), and adverse events was 2% in OPAT group vs 11% in IPAT group, (p=0·048). Length of stay was 4.3 days for the OPAT group and 5.5 days in the IPAT group (p=0.0019). Duration of intravenous antibiotics for the OPAT group was 2.2 days in OPAT group compared with 1.7 days in the IPAT group (p=0.045).
Ibrahim et al. (40) 2019b *RCT*	In children with cellulitis, treatment failure occurred in 1% patient in the OPAT group versus 8% patients in the IPAT group (risk difference –6·5%, 95% CI –12·4 to –0·7; p=0·029).
Ong et al. (37) 2019 *Cohort study*	In patients with cellulitis, the IPAT group had a higher incidence of acute renal failure compared with OPAT group (27.1% vs 3.8%, p=0.001), and nosocomial infection (10.4% vs 0.0%, P=0.023).
Rappo et al. (38) 2019 *RCT*	In patients with acute bacterial skin and skin structure infection, safety outcomes: rates of drug-related Treatment-Emergent Adverse Events (TEAEs), serious TEAEs, and TEAEs leading to premature discontinuation of study drug at 48-72 hour, days 14 and 28 were similar between OPAT and IPAT groups with either the single-dose or two-dose regimen.

[C0002]	Are the harms related to dosage or frequency of applying the technology?

Across studies, there were no differences in treatment length, duration of intravenous antibiotic therapy and medical care between the groups. It was indicated in the study of Ibrahim et al., 2019a (39) that the outcome length of stay favoured the OPAT group, whereas duration of intravenous antibiotic therapy favoured the IPAT group.

[C0007]	Are the technology and comparator(s) associated with user-dependent harms?

In the OPAT setting, where the antibiotic treatment is based on self-administration, there is a potential risk of user-dependent harms, which is not seen in IPAT (41). In all other OPAT settings, the administration of antibiotics is based on health care professionals with comparable education level between OPAT and IPAT. The studies included in this domain did not indicate any difference in user-dependent harms between the groups.

[C0010]	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

This issue is not discussed in the included studies. To compare IPAT with OPAT across heterogenic patient groups with various diagnoses, registries should collect data on complications related to the IV treatment itself such as catheter failure, infections or thrombosis to give a more precise measure of safety issues (42). Most of the studies reported only, whether the treatment worked on the infection or not, and it is too imprecise a measure to evaluate safety across the technology groups.

5.3 Conclusion

There are few safety concerns, when using OPAT instead of IPAT as a healthcare delivery model in treatment of patients with various diagnoses and outcomes. In the nine included RCT and observational studies, it was found that safety outcomes such as rate of treatment failure, serious adverse events, IV access complications and overall complications were low with no overall difference between the groups.

6 PATIENT & SOCIAL (SOC)

6.1 Research questions

Element ID	Research question
[H0200]	What are the experiences of living with the condition?
[H0100]	What expectations and wishes do patients have with regard to OPAT, and what do they expect to gain from this technology?
[H0006]	How do patients perceive OPAT?
[H0002]	What is the burden on care-givers?
[H0012]	Are there factors that could prevent a group or person from gaining access to OPAT?
[H0202]	How are treatment choices explained to patients?
[H0203]	What specific issues may need to be communicated to patients to improve adherence?

The SOC domain relates to issues relevant to patients, individuals and caregivers. They can provide unique perspectives about experiences, attitudes, preferences, values and expectations concerning health, illness, service delivery and treatments that can inform decision making about the implementation of OPAT. The SOC domain contains eight research question, which are listed above.

The patient is not just a passive target for interventions in health care. He or she is also a person with different roles – a family member, a citizen, an employee, a consumer, etc. The person may have many different spheres to the life: everyday life, homes, schools, workplace, health services, etc. The use of OPAT may place a burden on the patient or the carer (e.g. administering the treatment) or may change their everyday lives in both negative and positive ways. How patients and carers respond to, use and experience the technology is thus a vital aspect of assessing a health technology such as OPAT.

6.2 Methods

The comprehensive literature search identified 503 papers, which met the inclusion criteria for the overall assessment scope. Of these papers, ten met the inclusion criteria for the SOC domain. The inclusion criteria were:

- All conditions where patients and/or caregivers have experiences with outpatient parenteral antibiotic therapy (OPAT)
- Studies, that report first order patient and/or caregiver experiences, such as interview studies or surveys

The selection of papers was performed by two DEFACTUM researchers independently, using the Covidence software to structure the selection proces. Any disagreement between the researchers was solved by reaching consensus regarding inclusion or exclusion. This resulted in the inclusion of ten papers representing eight individual studies: Six qualitative interview studies, one survey and one systematic review.

The quality of the included papers was assessed using standard quality check lists. For the qualitative interview studies, the Standards for Reporting Qualitative Research (SRQR) checklist was used. The SIGN checklist for cohort studies was used for the survey, and the ENTREQ checklist for qualitative synthesis, was used for the systematic review. The quality assessment was performed by two DEFACTUM researchers independently. As the SRQR checklist does not contain a scoring system, the individual assessments were discussed by the researchers, and the study was subsequently assigned an overall quality assessment of high, moderate or low.

For data extraction and coding, all papers were imported into Nvivo 12 software for qualitative data analysis and coded according to the research questions. It was a deductive, analytical process, using the research questions as themes for the analyses. This deductive strategy was decided on after a preliminary read of the papers, which assured the researchers that all important findings were covered by the research questions. Thus, the data material consists of six codes with 13 to 63 coded meaning units in each. The codes were then read and discussed among the researchers and subsequently condensed to answer the research questions.

Generally, the included studies were of good quality, but the diversity in scope among the studies did not allow for a quality assessment of the included outcomes, such as a CERQual synthesis. Instead, the results are reported in a narrative format, highlighting the most important and common findings across studies, but also findings from individual studies, since some of the studies were the only one with a specific scope. The included studies are presented in Table 6 below.

Table 6: Study characteristics of the included studies

	Author, year and country	Stated aim	Stated design	Diagnosis (numbers in bracket)	Interventions	No. of participants (no. of interviews)	SRQR Quality Assessment
1	Berrevoets et al. 2018 Holland	Explore patients' needs and preferences for high-quality OPAT care, and to explore what 'patient-centred care' means to adult OPAT patients based on the eight Picker principles of patient-centeredness.	Qualitative study: Focus group interviews with patients and individual interviews with caregivers.	Infection in: Joint prosthesis (8) Urinary tract (1) Vascular prosthesis (5) Endocarditis (2)	OPAT with administration by a visiting specialist nurse. Not much detail about the intervention. Immediate access to hospital emergency department.	16 patients in 3 focus group interviews 2 care givers in individual interviews	Moderate
2	Minton et al. 2017 UK	To generate an understanding of patients' experiences of OPAT (and to use these to inform the development of a DCE)	Semi-structured interviews and focus group	Short term infection (20) Long term infection (12)	HO Attendance (14) Nurse at home (13) Self-administered (5)	28 individual interviews and one focus group (4 participants)	High
3	Mitchell et al 2017 UK	Evaluate evidence of the efficacy, safety, acceptability and cost-effectiveness of outpatient parenteral antibiotic therapy (OPAT) models.	Systematic review	Adult population treated for any condition (and or their carer for acceptability studies	Any form of IV antibiotic drug delivery system	128 papers of which 36 addressed patient acceptability of OPAT	High
4	Saillen et al. 2017 Switzerland	To evaluate the satisfaction of the patients treated by this new OPAT unit. In particular, to investigate if there is a difference in satisfaction between patients treated by home-care nurses, at the OPAT unit, or self-administering their antibiotics using elastomeric pumps.	Questionnaire	All patients treated at an OPAT unit	Self-administration (71) Attended OPAT unit daily (21) Home care nurse (20)	Of 188 questionnaires distributed to patients, 112 were returned	Low
5	Twiddy et al. 2017 England	Explore patients' experiences of OPAT services to identify issues, that affect patient experience and satisfaction.	Qualitative study: Semi structured interviews and focus group interviews with patients.	Not specified – a wide range of infections.	3 different interventions: 1)Hospital outpatient attendance 2) Nurse at home and 3) Self-administration	15 patients requiring short term (<7 days) IV antimicrobials 25 patients requiring long term (>14 days) IV antimicrobials	High
6	Tonna et al 2018 Scotland	To use a theoretical approach to understand the determinants of behaviour in patients, who are not home self-administering antibiotics.	Semistructured interviews	Spinal infection, Discitis, Knee septic arthritis, Hip prosthetic joint infection, Cellulitis in leg and elbow, Osteomyelitis in toe and tibia, Knee in-	1) Antibiotic administration by nursing staff in clinic 2) Antibiotic administration in community hospital 3) Home self-administration	20	High

	Author, year and country	Stated aim	Stated design	Diagnosis (numbers in bracket)	Interventions	No. of participants (no. of interviews)	SRQR Quality Assessment
				fection, Lung disease, Infective endocarditis, Infected cannula site, Infective endocarditis.			
7	Keller et al. 2019a USA	To learn how to best support patients and caregivers by characterizing patient understandings of patient, caregiver and health care worker roles in OPAT and barriers to fulfilling these goals.	Semistructured Patient telephone interviews and contextual inquiries of patients and caregivers performing OPAT–related tasks at home (medication infusion, VC care, and so forth)	Not specified.	Not specified. Different home infusion and home care agencies.	40 patients in semi structured interviews and 20 patients in contextual inquiry.	Moderate
8	Keller et al. 2019b USA	An in-depth understanding of how the home environment hinders safe performance of OPAT related tasks, and how patients mitigate these safety hazards.	Semistructured Patient telephone interviews and contextual inquiries of patients and caregivers performing OPAT–related tasks at home (medication infusion, VC care, and so forth)	Not specified.	Not specified. Different home infusion and home care agencies.	29 patients in semi-structured interviews and 14 patients in contextual inquiry.	High
9	Carter et al. 2020 UK	To better understand the factors that facilitate and hinder a positive experience of paediatric outpatient OPAT.	Qualitative study: Parents, who had participated in the survey phase of the larger study were invited to be interviewed.	Perforated Appendix (1) Chest Infection (2) Sepsis (1) Pneumonia (2) Meningitis (1) Occular Cellulitis (2) E.Coli Septicaemia (1)	Hospital-based, outreach OPAT service, with community nurses visit once daily to administer medication, and 24-hour telephone support is also available.	12 parents of 10 children and one child of 15 years. (n=33).	High
10	Keller et al. 2020 USA	To 1) perform a goal-directed task analysis of patient and caregiver-performed OPAT and 2) through the identified goals, describe associated hazards to and strategies for the successful performance of OPAT	Semistructured Patient telephone interviews and contextual inquiries of patients and caregivers performing OPAT–related tasks at home (medication infusion, VC care, and so forth)	Not specified.	Not specified. Different home infusion and home care agencies.	40 patients in semi structured interviews and 20 patients in contextual inquiry.	Moderate

6.3 Results

[H0200]	What are the experiences of living with the condition?

With this technology, multiple conditions are in play and they are often short-termed or temporary. There is nothing in the SOC literature about living with the different underlying medical conditions.

[H0100]	What expectations and wishes do patients have with regard to OPAT and what do they expect to gain from this technology?

A total of five papers from four individual studies addressed the issue of patients' expectations toward OPAT and being treated at home . Generally, many patients have a perception that recovering at home is better than at a hospital, and that there is less chance of getting an infection in the home. Some patients though, are worried about experienced problems with the equipment. It could be obstruction of the Picc-line, problems with the pumps, storage of medicine etc. (43-45). For some patients, this leads to a desire to learn about the tasks connected to OPAT in more detail (46). Patients, who are expected to self-administer express more worry before initiating the treatment, than patients treated in OPAT units or by home nurses (44). Most patients expect some kind of assistance form the health care system, if they are to be treated at home (47).

[H0006]	How do patients perceive OPAT?

A total of ten papers and seven studies addressed the perceptions of OPAT from the patients' perspective. One of the most appreciated aspects of OPAT is the possibility to enjoy the comforts of the home and not being disrupted in daily living (22, 44, 45). There is a feeling of freedom and normality connected to being at home (48, 49). Comparing the different models for OPAT, there is a tendency towards perceiving home treatment more convenient and less stressful than receiving daily treatment at the hospital or in an outpatient clinic (22, 45). In the study of Keller at al., some patients express gratitude towards their caregivers and emphasise that being treated at home increases awareness of the value and importance to have helping caregivers, which could strengthen the patient-carer relationship (47). Carter et al.'s study on parents with children in OPAT found that being treated at home makes it possible for the whole family to be together and for the routines of everyday life to be resumed. This way, it is easier to be a family and they feel more cosy at home. The families feel, that they can regain control over decisions in everyday life, like bedtimes, mealtimes and other daily activities. Some of the parents feel that their stress level decreases by being at home (49).

To move treatment from the hospital to the home environment creates some level of worrying among a group of patients. First of all, not having medical staff around can increase worry and some patients struggle to find a sense of security at home. Some have considerations about the home as a site for treatment, such as 'is my home clean enough to function as a treatment space?' (49). For some patients, it is their first time with a port in the arm for treatment and this "arrangement" is unfamiliar and anxiety-provoking. These patients wish for the health care professionals to recognise and acknowledge this anxiety (22, 43). In these cases, it can be reassuring if the patients know that the hospital is ready to help with information and advice. Likewise, it is

important with good communication between the hospital and community to create security and continuity (49). Some patients have experienced, that it is difficult to imagine how hard it is to take care of one self, following discharge from hospital and as a consequence many patients are dependent on caregivers to help with daily activities. This dependency is at times frustrating and can force the patients to change their daily activities. Therefore, they stress the importance of being aware of the situations in the patients' home and the patients' life, before discharging to OPAT (43) (47) (50).

One of the few negative perceived consequences of OPAT is that everyday life has to be adjusted around the hours for treatment, which can make it difficult to find time for anything else. Sometimes, it feels like waiting for the nurses endlessly (43, 45, 46, 49, 50). Also, for patients with continuous antibiotic infusion, their daily activities are strongly influenced by the OPAT. It can be everyday activities like taking a bath or it could be going on a trip. Tiredness as a consequence of the treatment could also prevent patients form participating in social activities (48).

If OPAT is performed in the home by visiting nurses, most patients prefer to see the same nurse every day, or a small team of nurses. If the nurses are different persons from time to time, the patients are unsure, if the new nurse is familiar with the treatment plan etc. Due to the potential anxiety connected to OPAT and the feeling of waiting for the nurse all day, a delay in the nurse visit can create worry and frustration among the patients (45). Likewise, if the patient is treated at a clinic, it can create a lot of frustration, if they are not given an exact time for treatment, but instead a time slot. It is very much appreciated when time for treatment at hospital or clinic can be fitted around the patients' other activities (45). Getting to the hospital or other outpatient facilities are for some patients perceived as troublesome. It takes a lot of time, it is difficult to travel with a cannula in the arm and parking can be difficult and expensive. Some patients also have to involve caregivers in the transportation (45, 51). On the other hand, some patients perceive treatment at the hospital as reassuring because of the security of having a physician around, if something goes wrong (45). Other studies have found that OPAT patients receiving treatment in the home finds the nurses very professional and attentive to the patient and caregivers needs, which creates a feeling of security (48, 49).

[H0002]	What is the burden on care-givers?

A total of seven papers from five individual studies addressed this question. As none of the papers has burden of caregiver as main study aim, the evidence is indirect and we have elicited information about experiences that could be perceived as potentially burdensome. One study (49) investigate the experiences of parents of children, who receive OPAT and finds home-based concerns to be minor and manageable, and mainly related to the line/the port. However, another study finds that caregivers can be concerned about the IV and correct management (51) and that patients sometimes prefer to have caregivers present during their infusion, even if this person is not actively involved (45). The role of the caregiver and the associated workload are not always clearly communicated to caregivers (47), and sometimes caregivers may underestimate the time and high-skilled tasks required for managing OPAT on a daily basis. For example, in cases of elderly patients, the caregiver may be required to – temporarily – live with the patient (47). OPAT patients stressed the value of caregivers, as they relied on their practical and emotional support (45, 51). This support included practical assistance with the OPAT (46), searching for information online (48), participating in doctor-patient conversations (47, 48), or assisting with transportation or shopping. However, as none of the included studies explicitly address the potential burden that caregivers may experience, we cannot conclude if these tasks are considered more or less burdensome.

[H0012]	Are there factors that could prevent a group or person from gaining access to OPAT?

Five papers from three individual studies addressed this research question. For some older patients, OPAT may be unsuitable as the general health and level of mobility can be a barrier for treatment (22, 45), e.g. arthritis or visual impairment making it difficult to handle the technology (47). Also, family circumstances and social resources should be considered before initiating OPAT, e.g. access to carer and informal help. Generally, infusion at the hospital or in a clinic can be challenged by public transport but also transport time in general and lack of parking (43, 45, 51). Finally, concern about consequences and lack of confidence in the ability to take care of own treatment may also prevent some groups from gaining access to OPAT (51).

[H0202]	How are treatment choices explained to patients?

A total of nine papers from eight individual studies addressed this question. Though many patients feel adequately informed about OPAT treatment at home, in three studies patients report that the decision was made without involving them or their relatives (48, 49, 51). Some patients feel that this violated their autonomy (48), while others are content with delegating the decision to a health care professional based on an understanding that 'the doctor knows best'. In some studies, patients receive adequate written and oral information (44, 48, 49), whereas in other studies the procedures are not always well-explained (46-48). Keller (46, 47) suggested that low health literacy can be a barrier as patients do not always understand medical terms and written information, but may prefer face-to-face instructions and pictograms. Keller (2020) (46) identified barriers to sufficient information about treatment choices: Misleading or contradictory information, rushed instructions and confusing manuals. In some studies, patients indicate that they would have wanted more information about the antibiotics, the possible side effects and interactions (45, 48), and have little recall about information about adverse effects (49). In the study by Minton et al. (45), the patients are not overly concerned with the lack of information as long as treatment progresses. However, when recovery is not as expected, the lack of information become more significant and patients feel that they have been left in the dark about their treatment options. In the study reported by Minton (45) and Twiddy (43), patients value to be given a named point of contact that can be reached if questions arise. This ability to ask question before and during treatment empower patients to be actively involved in their own care and make OPAT at home a meaningful and safe choice.

[H0203]	What specific issues may need to be communicated to patients to improve adherence?

A total of eight papers representing five studies addressed this research question and show, that important topics to communicate to patients are:

- Potential antibiotic side effects
- Instructions for use and skills training
- Information about intravascular access devices
- Potential complications and how to handle them

- Information about treatment progress

In the studies by Keller (46) (50) (47, 50), patients request advise or input on how to deal with everyday practicalities during OPAT, such as gardening, showering or caring for a pet. Also, in the studies of Berrevoets and Keller, patients lack information about the level of hygiene needed and how to achieve it.

Central in several studies is that it needs to be clearly communicated to patients, who they can contact in case of problems or questions(43, 45, 47, 48, 51) . Clear communication pathways and being able to contact the OPAT team between appointments provided assurance of good care (45, 51) made patients feel secure (47, 48) and supported effective self-management (45).

Also, future appointments, midterm checks and end-of-care appointments must be clearly communicated to the patient, as lack of clarity about what should happen next, causes uncertainty (43). Finally, it is important that the different staff involved in OPAT communicate between themselves, as lack of inter-staff coordination and mixed messages creates worry and uncertainty for patients.

6.4 Conclusion

As mentioned above, the results about patients' perspectives on OPAT are based on nine qualitative studies and one survey study. Six qualitative studies were rated as high quality and three as moderate quality, using the SRQR assessment. The survey study was rated as low quality, using the SIGN checklist. Taken together, the studies are of acceptable quality, but the small amount of studies and the diversity of the included population and interventions make it difficult to make conclusive statements about specific patient groups. The conclusions emphasised below are those presented as important across several studies.

One point is the importance of selecting the right patients for OPAT. Going through OPAT can be a demanding process, and therefore it is important to assess the patient's home situation, as some patients will very much depend on caregivers/external help for OPAT to be a success. Important factors to consider before initiating OPAT are; patients' mobility in general, comorbidity, family circumstances, social resources, care giver resources', the condition of the home etc. It could therefore be relevant to develop tools for shared decision making or screening tolls to identify the patients who have the resources to successfully manage OPAT.

One of the most appreciated aspects of OPAT is the possibility to enjoy the comforts of the home. Being at home increases the feeling of freedom and normality. For children being treated with OPAT, being at home is a chance for the whole family to be together. Likewise, it is expected that being treated at home reduces the risk of infections. However, moving treatment from the hospital to the home can sometimes create worry and fear of complications. A reassuring factor is knowing who to contact in case of questions or needed assistance. Generally, the ability to ask questions before and during treatment empowers patients to be actively involved in the treatment. Clear communication about the course of treatment, practicalities, possible side effects and what to expect from OPAT, altogether create a feeling of security. Information about treatment is always appreciated but especially when treatment does not progress as expected. To be an OPAT patient, generally takes up more time than expected as everyday life has to be adjusted around the treatment. Nevertheless, most patients prefer treatment at home compared to inpatient treatment. Following this conclusion, it is important to remember that most patients in the included studies only have experiences with one of the treatment pathways. Therefore, they are not able to compare the different treatment pathways, but express a general desire to be treated at home.

7 ORGANISATIONAL (ORG)

7.1 Research questions

Element ID	Research question
G0001	What characterizes the work processes related to OPAT?
A0012	What kind of variations in use are there across regions and municipalities?
A0025	How is OPAT currently managed according to published guidelines and in practice?
G0009	Who decides, which people are eligible for OPAT and on what basis?
G0004	What kinds of co-operation and coordination of activities have to be mobilized across professionals and sectors?
G0003	What kind of process ensures proper education and training of staff in hospitals and municipalities in relation to use of OPAT?
G0008	Which organisational challenges and opportunities are attached to the use of OPAT?
Added question	Which organisational perspectives can be pointed out in relation to the future use and dissemination of OPAT?

The aim of the analysis of organisational aspects is to describe the organisational preconditions and consequences of using Outpatient Parenteral Antibiotic Therapy (OPAT) compared to Inpatient Parenteral Antibiotic Therapy (IPAT). This includes description of organisational structures and work processes related to OPAT and the co-operation across sectors and professionals, as well as description of education and training requirements for using the OPAT. Moreover, the analysis seeks to identify organisational challenges and possibilities of using OPAT compared to IPAT, and point to organisational perspectives in relation to the organisation of future use of the OPAT. Research questions for the analysis are outlined above.

Below, the methodological approach to the organisational analysis is outlined. Subsequently, the results of the analysis are presented by answering the listed research questions. The presentation of results is structured in two parts. In *Part One* the current organisation of OPAT in Denmark is described. This includes a presentation of existing guidelines, co-operation agreements and other regulation of the organisation of OPAT (A0025), a description of the delivery models and work processes related to OPAT (G0001, A0012, G0009), a description of the inter-professional and inter-sectorial co-operation and coordination related to OPAT (G0004) and a description of education and training requirements and processes in place for the staff involved in the delivery of OPAT (G0003). *Part Two* presents the identified organisational challenges and possibilities associated with the use of OPAT, including organisational perspectives on future use and dissemination of OPAT (G0008, Added question). Finally, conclusions of the analysis and discussion of the methodological approach are presented.

7.2 Methods

The organisational analysis combines a systematic literature review (see Domain 2 for description), a document review and a qualitative interview study. The triangulation of methodological approaches ensures a more thorough and valid analysis. Where the literature review helps to provide an overview of international experiences regarding the use of OPAT, the document review provides insight into the formal organisation of OPAT in a Danish context. Finally, the interview study provides knowledge on how OPAT is organised and delivered

in practice across regions, hospitals and municipalities as well as on the organisational challenges and opportunities associated with the use of OPAT. Also, the literature review and the document review contribute to identify essential organisational aspects to be further investigated in the interview study.

Document review

In the document review relevant available local, regional and national documents and guidelines for implementation and use of OPAT in Denmark were examined. The documents included in the analysis were identified through internet searches, including regional and municipal websites. Furthermore, relevant documents were identified through dialogue with regional and municipal staff. The inclusion and exclusion criteria in the document review were similar to the criteria in the literature review (see Domain 2).

Qualitative interview study

The interviews were conducted as explorative, semi-structured interviews with informants from different regions, hospitals and municipalities. This enabled us to identify differences and similarities across hospitals, regions and municipalities. In the interview study, we included hospital physicians and/or nurses from five hospitals (one hospital in each region, n = 8) and a regional administrative employee from each of the five Danish regions (n = 5). Furthermore, we included municipal nurses and municipal leaders/administrative employees representing five different municipalities (n = 10). The interview informants were chosen as they represent different perspectives on the use of OPAT and thus together provide a thorough perspective on the research questions.

The selection of municipalities was based on a 'best cases' criterion, meaning that included municipalities had a certain volume of OPAT patients and thus a certain experience with handling the patient group and organising the treatment. Regarding hospitals, we have included informants from both large size and small size hospitals. Moreover, we included informants from hospitals and municipalities which collaborate in relation to OPAT patients. Regional and municipal employees have assisted in the identification of relevant informants. Table 7 provides an overview of the included informants. Appendix 2 provides a more nuanced overview of both invited and participating informants.

Table 7: Overview of interview informants

Informants	Number
Regional administrative employees	5
Hospital physicians	4
Hospital nurses	4
Municipal leaders/administrative employees	5
Municipal nurses	5
In total	23

The interviews were performed as focus group interviews or individual telephone interviews. Primarily, the focus groups were composed of interview informants from the same unit, however, some of the informants from different municipalities (within the same region) were interviewed together in one focus group. All interviews were guided by semi-structured interview guides with open-ended questions (52). The interview guides were informed by the research questions, the literature review and the document review, and developed in close co-operation with the project group. The interview guides are presented in Appendix 3. The interviews

lasted approx. 1-1½ hours. All interviews were digitally recorded and transcribed verbatim. The interviews were analysed using a thematic approach (53).

7.3 Results

Results of the systematic literature review

The result of the systematic literature search and the selection process, including the in- and exclusion criteria guiding the process, is described in 'Methods and evidence included' (Domain 2) and presented in the flowchart (Figure 1).

Characteristics of included studies

Twelve studies were included in the systematic literature review on organisational aspects. The twelve studies are presented in Appendix 4 with regards to aim, study design and methodological approach, main results and quality assessment. The studies are published between 2012 and 2020 in the Netherlands (54), Belgium (2), the United Kingdom (3, 5-7, 55) and the United States (4, 56-59). Study designs include literature reviews (2-5, 7, 54, 55, 57), expert assessments (6, 56, 58) and a literature review combined with 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) (59). The results of the studies primarily focus on the importance of ensuring certain practices within OPAT services to provide safe and effective care. Largely, these regard the OPAT care team, patient selection and monitoring, patient- and caregiver education, antimicrobial management, service structure, and clinical governance. The results are elaborated in the following sections.

Common for the included studies are that the perspectives and arguments expressed remain on a general level and the studies are primarily literature reviews. In the presentation of the literature, focus will be on the results that are considered most relevant in a Danish context, as organisation of and processes within health care systems to varying degrees differ across national contexts, and thus potentially also in relation to implementation and use of OPAT. As such, the national context of the included studies may impact the transferability and generalisability of the results in a Danish context.

Results of the document review

The most essential documents in the document review are the co-operation agreements between regions and municipalities which outlines the division of roles and responsibilities in relation to OPAT. In addition, the document review examines central national documents including the current clinical guideline in internal medicine, infectious diseases (Specialevejledning for intern medicin, infektionssygdomme) (60), the Danish Health Care Act (Sundhedsloven) (61), the Regional Healthcare Agreements (Sundhedsaftalerne)(62-66), and the Danish Health Authority's current quality standards for municipal acute functions (67). Relevant local and regional guidelines are also included.

Common for the selected documents are that they affect the framing and formal regulation of OPAT and/or describe the work processes related to OPAT. The regions which do not have a specific co-operation agreement with the municipalities on OPAT have instead defined a number of local agreements. We have prioritized not to include these documents in the analysis due to limited resources.

Part One: Current organisation of OPAT

G0001	What characterizes the work processes related to OPAT?
A0012	What kind of variations in use are there across regions and municipalities?
A0025	How is OPAT currently managed according to published guidelines and in practice?
G0009	Who decides which people are eligible for OPAT and on what basis?
G0004	What kinds of co-operation and coordination of activities have to be mobilized across professionals and sectors?
G0003	What kind of process ensures proper education and training of staff in hospitals and municipalities in relation to use of OPAT?

The organisation of OPAT is in a Danish context characterized by great complexity and variation. Thus, the following description will be focusing on the overall picture of the organisation of OPAT. Even though the collected empirical material does not allow for a systematic overview of similarities and differences, as the analysis only includes a sample of hospitals and municipalities, identified regional and municipal variations will be highlighted. The presentation is based on a combination of data collected from the literature review, the document review and the qualitative interview study.

Formal regulation of OPAT in a Danish context

Generally, OPAT is delivered in co-operation between the regions (hospitals) and the municipalities in their regions. The planning and organisation of OPAT is handled within the regions and is regulated by multiple co-existing political-administrative and legal frameworks on both national and regional level. This next section describes the central national documents with implications for OPAT and co-operation agreements between hospitals and municipalities.

It appears from the existing clinical guideline in internal medicine, infectious diseases of June 4th, 2018 that municipalities and regions are obligated to ensure coherence and coordination of treatment in inter-sectorial patient trajectories, framed by the Regional Healthcare Agreements (68-72). This for example applies to patients in needs of lengthy parenteral antibiotic therapy. In relation to this group of patients, the clinical guideline specifies that with sufficient supervision and monitoring from the hospital they can receive their treatment at home or in local care facilities. In these cases, the treatment is performed on delegation from the hospital physicians. It appears from the clinical guideline that this type of 'shared care' is only expected to increase in both extent and complexity in the next few years (60).

Co-operation agreements between hospitals and municipalities

Across regions, OPAT has until recently been organized and regulated by local agreements of varying degrees of formalization between the hospitals and the municipalities. However, during the last few years the regions have started to develop and implement more formal co-operation agreements between the regions and the municipalities. The stage of development and implementation of the agreements varies between the regions. While the Region of Southern Denmark has had a co-operation agreement since 2017 (72), an agreement has been developed during 2020 in Central Denmark Region (69) and the North Denmark Region (70). The implementation of the agreements in these two regions is still on-going. In the Capital Region of Denmark and Region Zealand there are currently no co-operation agreements on OPAT. However, OPAT is in these regions included in existing broader agreements on delegation of tasks and continuity of patient care across hospitals and municipalities (68, 71). The commitment to the co-operation agreements on OPAT is currently optional for the municipalities. The existing co-operation agreements for each region are displayed in Appendix 5.

In general, the purpose of the co-operation agreements on OPAT is to give patients the opportunity to receive parenteral antibiotic therapy in their own homes or in care facilities in their local community. The agreements support a planned and coordinated delegation of tasks across sectors. Furthermore, the agreements aim to ensure a standardized practice across hospitals and municipalities. The target population of the co-operation agreements is patients in IV treatment with non-hospitalization needs for treatment, who are stable and assessed suitable by a physician to complete the treatment at home or in the local community. It varies whether children are included in the agreements. In addition, it varies whether the co-operation agreements are particularly related to parenteral antibiotic therapy or include other types of parenteral treatment as well. Thus, while the co-operation agreement of the Region of Southern Denmark particularly concerns OPAT, the agreement from Central Denmark Region covers antibiotics and isotonic fluids and the agreement form North Denmark Region covers parenteral treatment in general.

A central task of the co-operation agreements is to establish the division of responsibilities between the region (hospitals) and the municipalities. Across the regions' agreements it appears that the hospitals hold the medical treatment responsibility for patients receiving OPAT. This responsibility includes offering relevant patient education and information, initiation of the relevant type of treatment, preparation of treatment plan, delivery of medicine, offering hot-line counselling to municipalities, monitoring and termination of treatment. The municipalities hold the responsibility for training municipal nurses in intravenous medicine administration. In addition, the nurses must possess the relevant clinical qualifications and carry out the treatment plan prepared by the hospital. Across regions the agreements state that the patient's general practitioner bears no responsibility in relation to OPAT initiated at the hospital. It varies whether a financial framework for OPAT is part of the co-operation agreements (see Domain 8 for further description).

Education and training of OPAT nurses in the municipalities are also specified in the co-operation agreements. Handling OPAT requires a nursing background and cannot be delegated to other professionals. In the North Denmark Region, the hospital offers to facilitate training and education of nurses, while the Region of Southern Denmark and Central Denmark Region consider it a municipal responsibility to ensure the required qualifications of the nurses involved in OPAT. In some regions, patients are offered to be trained in self-administration of OPAT by the hospitals.

In addition to the co-operation agreements, OPAT is organised and regulated on the basis of different regional and local guidelines, e.g. in relation to specific work processes, self-administration and shared decision-making regarding OPAT. It varies between hospitals, regions and municipalities which guidelines are available. Some of the relevant guidelines will be presented in the following sections. Also, a number of quality standards have been established by the Danish Health Authority to support high quality in interventions delivered by municipal acute functions. The quality standards include requirements concerning content and preparation of the municipal acute functions in home nursing care such as treatment responsibilities, competency development, and municipalities' access to utensils and medicine. However, it is worth mentioning that not all municipalities use the municipal acute functions in the delivery of OPAT (67).

Patient trajectories in OPAT

The following sections describe the practical organisation and structure of the patient trajectories in OPAT, including visitation and initiation of OPAT, transition of care, monitoring and termination of treatment. The description will address the various OPAT delivery models as well as the inter-professional and inter-sectorial co-operation and coordination in the different phases of the patient trajectory.

Patient selection and initiation of OPAT

The majority of hospitals and municipalities in the interview study provide OPAT for in average 1-9 patients per month, however, the number of patients varies. Only one hospital handles 20 OPAT patients or more per month. In some hospitals, only a few selected departments are able to refer patients to OPAT, while in other hospitals, several (or all) departments refer patients to OPAT.

The interview informants describe that once a patient is stable for discharge but continues require IV antibiotics, OPAT is an option if the patient is assessed as a "good candidate". The selection of OPAT candidates is often described as an informal collaboration between the different professionals at the hospital (physicians, nurses, microbiologists). Microbiologists provide the necessary test results as well as an assessment of the duration of treatment. The patient must be willing to comply with the treatment plan and the patient's home or outpatient environment must be safe and adequate to support the treatment. If relevant, it will then be clarified with the municipality whether they can receive the patient. Informants from one of the municipalities in the interview study mention, that nurses from the municipal acute unit often visit the patient at the hospital in order to make an assessment of the patient's suitability for OPAT. Finally, the informants point out that it is essential that the patient is involved in the decision making and feels safe. In one of the regions, a tool for shared decision making is used (a part of a regional guideline for OPAT) in which risks and benefits related to OPAT is outlined to the patient. The interview study reveals, that most patients receiving OPAT in Denmark are elderly or middle-aged medical patients, though a few hospitals include children. Typical infections treated with OPAT regimes are described in the 'Technology section' (Domain 3, TEC).

Similar procedures for patient selection are found in the international literature. However, in other countries OPAT is often initiated and supported by a formal OPAT care team at the hospital (see 'OPAT delivery models', Domain 3), including e.g. an infectious disease (ID) specialist; a nurse with expertise in OPAT; and a clinical pharmacist. The composition of OPAT teams varies and team members can be combined across sectors. In some hospitals, the patient is considered a member of the OPAT team as well (2-6, 54-56, 58). Several studies highlight the importance of clear guidelines or protocols for patient selection (2, 5, 6, 54, 55, 57). According to the UK Good Practice Recommendations for OPAT, patient selection has 5 key components: 1) An ID specialist should determine inclusion and exclusion criteria for specific infections; 2) Standardized and documented patient suitability criteria should incorporate physical, social, and logistic elements; 3) A member of the OPAT team should provide an initial assessment of patient suitability; 4) Patients and caregivers should be fully informed of the risks and benefits of OPAT and have the opportunity to decline OPAT; 5) If the patient is at risk of deep venous thrombosis, ongoing prophylaxis should be considered (55, 57). Despite different organisational models for the execution of OPAT in an international context, there is a joint focus on selecting the right patients for the right treatment paradigm. The UK Good Practice Recommendations for OPAT is just one way to conceptualise this selection process and it can take many other forms. The important point is to be aware of selecting patients suitable for OPAT.

Transition of care and monitoring

Once the decision has been made, the Danish guidelines and the interview study show that the hospital physicians then prepare the treatment plan including duration of treatment and monitoring.

If the patient is treated at home or in the local environment, the referral is prepared and the relevant type of medicine, information material and medical devices are packed. The required medical devices are identified in collaboration with the municipality, if they are involved in the treatment. At one hospital, a specific integrated discharge team is responsible for the practicalities regarding the referral of OPAT patients (among other patients). The team is described as 'specialists in inter-sectorial co-operation' and consists of experienced nurses,

physical therapists and hospital based social and healthcare assistants. Presumably, the team cannot be compared to the OPAT teams described in the international literature, as there is no physician in the team and the team does not bear a treatment responsibility. The amount of medicine prescribed for OPAT patients depends on e.g. the patient's condition and the expiration date of the medicine. The duration of treatment varies from 3-5 days to 1-3 weeks. Some of the interview informants state that the patient will only receive medication for one full day at a time, not risking to ordinate medication, that otherwise will not be used, if the patient completes the treatment faster than expected. In these cases, it is either the municipality or the patient/relative who picks up the medication at the hospital. Elsewhere, standard procedure is for the patient to receive medication for one week at a time.

In the next step, patients are transferred to the chosen outpatient setting. At some of the hospitals, the outgoing team occasionally help to install the medical devices in the patient's home and initiate the treatment. Progress in the patient's condition is closely monitored and the medication is adjusted if necessary. Across hospitals and municipalities, the interview study reveals a variation in monitoring practise of the OPAT treatment, depending on the chosen delivery model. Generally, the OPAT patients are examined by a physician at the hospital e.g. once a week. In addition, most patients are monitored outside of the hospital in various ways. In one of the hospitals represented in the interview study, the patient is provided with a device for home monitoring to measure infection rate and temperature. Furthermore, the patient is using a tablet to answer questions about side effects, well-being and safety. The answers are automatically reported to the hospital and a nurse reviews the answers. In other regions the outgoing team from the hospital or the municipal nurses are responsible for regular monitoring of the patient outside the hospital. The patient's physician at the hospital is to be consulted when relevant.

In accordance with the interview study, the international literature stresses that continuous communication and a clear treatment plan are essential for the transition of care in the OPAT trajectory to succeed (4, 57). Furthermore, the literature recommends regular monitoring of the patient as a part of the treatment plan. Depending on the patient's condition, it is recommended that the patient is monitored (e.g. blood tests) daily or 1-2 times a week. Twice-monthly clinical reviews are presumed to be sufficient for patients in long-term OPAT treatment. It is recommended that the precise frequency of the monitoring should be decided locally (3-7, 54-58). Due to the large variation in the organisation of OPAT in and across countries, there are no universal recommendations on how the monitoring should be organised and which health care professionals should be involved. However, several studies suggest that the monitoring is best handled by a specialised team (3, 5, 54, 55, 59). So the literature points to the importance of monitoring patients included in OPAT strategies, but the relevant monitoring strategy is very much dependent on local conditions. Who should be monitoring what and what it is necessary to monitor, will vary on the organisation of the treatment. This variation is also present in a Danish context, as described above.

Moreover, the literature emphasises the importance of monitoring of quality assurance outcomes in relation to OPAT. It is recommended that OPAT outcomes should be collected prospectively and recorded in a local database. Outcome measures can include treatment completed as planned or reason for non-completion, readmission rates, adverse drug reactions, vascular access complications etc. According to the literature review, the monitoring of outcomes is essential for continuous performance improvements (3, 5-7, 54-57). The interview study reveals that systematic outcome monitoring is typically not performed on Danish OPAT patients. Some interview informants mention that quality assurance of the OPAT trajectories is part of the treatment, but a systematic procedure for registration is missing. Other interview informants state that the current focus is on the implementation of OPAT, and therefore they have not yet established a system for outcome monitoring. A gathering of local experiences with OPAT in Denmark is about to be established in some of the regions.

End of therapy

If patients show satisfactory response to OPAT, the treatment is either completed or switched to oral antibiotic. The interview study identifies different models for patient follow-up. However, it is always the physician responsible for treatment who determines the need for follow-up. The informants describe, that in some of the less complicated patient cases, only a few days of OPAT is needed for the patient to complete the treatment and no further follow-up is necessary. In some regions, the outgoing team from the hospital has the authorisation to complete treatment in the outpatient setting, in consultation with the hospital physician responsible for the treatment. Across hospitals in the interview study, it is standard procedure that the municipality and the patient's general practitioner are notified when OPAT is completed.

The literature describes different dilevery models for OPAT in an ambulant hospital setup (see Domain 3). This is also seen in Denmark, but the interview study shows that OPAT in an ambulant hospital clinic is used to a very limited extent in the hospitals included in the interview study. Several interview informants state that ambulant treatment is not a part of their OPAT setup, while other interview informants describe that approx. 3-5% of OPAT patients receive ambulant treatment. These are primarily patients who only need one daily infusion or patients who receive treatment through pumps that need to be changed daily. However, the interview study reveals that ambulant treatment is increasingly used in a hospital in the North Denmark Region and they are planning to establish an ambulant hospital clinic with specific treatment responsibilities. Currently, one of the departments at this hospital has up to 30% of OPAT patients in ambulant treatment. These are primarily patients with infections that require longer treatment. In line with the interview study and the document study, the international literature has very limited descriptions of the specific organisational aspects of ambulant treatment of OPAT patients.

Inter-sectorial co-operation and coordination

This section describes the division of responsibilities and communication between the hospitals and the municipalities from the interview informant's point of view. This only concerns the two of the OPAT delivery models where the municipality is involved.

Division of responsibilities

Across the interview study, there is a general consensus regarding the division of roles and responsibilities between region and municipalities.

According to the interview informants, the hospital physician holds the medical treatment responsibility for patients receiving OPAT, as described in most of the co-operation agreements. In practice, this means that if the hospital e.g. is contacted by a patient or the municipality in case of challenges in the OPAT-program, the hospital physician is expected to guide the solution. The hospital physician is responsible for the treatment plan, including the correct amount and duration of treatment as well as updating the Shared Medication Record (FMK). Several of the nurses in the interview study define themselves as the main coordinator in the OPAT trajectory. They inform the patient, ensure the necessary appointments with the municipality (if relevant) and pack the medical devices. The informants describe that it lies within the hospital's responsibility to provide the necessary medication and medical devices as well as ensuring a counselling hot-line for patients and municipalities. The hospital is also responsible for patient education in case of self-administration. Finally, the hospital is responsible for the patient follow-up, replacement of medical devices and adjustment of medication. It is always the physician who makes the final decision to complete treatment.

Once the municipality has accepted to receive the OPAT patient, it is the municipality's responsibility to provide an organisational setup to support OPAT. According to the interview study, the municipality choose the optimal solution for each OPAT patient, depending on the current capacity. The interview informants describe that the

municipality has an executive role in a regional task. However, still the medical treatment responsibility lies within the operating physician at the hospital. The municipality is responsible for following the treatment plan and observation of the patient. The municipal nurses (or an assistant) administer and maintain the medical devices during the OPAT trajectory and they make sure that the devices are properly taken down at the end of treatment. Furthermore, it is the municipalities responsibility, that the nurses possess the relevant clinical qualifications to handle intravenous treatment (see 'Education and training' below).

The establishment of a solid interdisciplinary co-operation between hospitals and municipalities but also involved physicians, nurses, patients and care-givers is perceived as an important precondition by the interview informants to ensure proper OPAT treatment. In general, the interview informants perceive the co-operation between hospitals and the municipalities as successful. In concordance with the co-operation agreements, informants across sectors state that the patient's general practitioner has no responsibility in relation to OPAT. However, the role of the general practitioner can be questioned if for example the patient's condition is deteriorated (with no relation to the infection), while the patient is at home. In such cases, it is usually the hospital that bears the full responsibility as longs as the patient is in the OPAT program. This issue is a subject of discussion in several regions.

Communication

The interview study shows that the initiation of OPAT is the most important part of the patient trajectory in terms of communication and clarification between the hospital and the municipality. Usually, the necessary agreements are made one day in advance. In some patient cases, there is a continuously daily contact between the hospital and the municipality. The interview informants from both hospitals and municipalities describe that the hospital is available 24-hours a day if needed. Occasionally, a discussion of alternative treatment plans is required, depending on the development of the patient's condition. If there is an unexpected progress in the condition or if changes in the treatment plan occur, the hospital and the municipality discuss the next step. If OPAT is completed without complications, no further communication is needed, besides a written notification from the hospital at the end of treatment.

As demonstrated in the above, the municipality and the hospital communicates verbally as well as in writing. Some of the local OPAT guidelines state that in order to avoid misunderstandings, the cross-sectorial communication must be done verbally over the phone (at least during the initiation of OPAT). Sometimes, the patient automatically acts as a link of communication between the hospital and the municipality.

Generally, the interview study reveals that proper and clear communication amongst involved health professionals across municipalities and hospitals is requisite for achieving high efficiency and coherent continuity of care.

Education and training

Below, training processes and competency development of hospital and municipal nurses are described. The descriptions are primarily based on the interview study and the document review, as the brief and general recommendations of the literature review do not specify, how training processes and competency development should be organised.

According to the literature review and the interview study, the ensuring of a successful OPAT service requires that nurses, within hospitals and communities, have the necessary skills and competencies to manage OPAT. In order to ensure this, nurses might require training or competency development in managing OPAT(3, 6). Continuous competency development and training is perceived as a precondition to ensure proper OPAT treatment by some of the interview informants. In addition, the interview study reveals, that the extent and

necessity of OPAT training and competency development amongst nurses varies across hospitals and municipalities.

In a Danish context, hospital departments provide their staff with continuous competency development and training or instructions in managing OPAT. With regard to municipal nurses, the majority receive some sort of training and competency development prior to the handling of OPAT. However, the interview study reveals, that a considerable proportion of the municipal nurses already have the skills required to handle OPAT treatment, while others emphasise a great need of competency development due to inexperience or limited knowledge of OPAT. Hence, the need of OPAT training and competency development amongst municipal nurses varies greatly depending on the local organisation of OPAT.

According to the interview study and the document review, essential skills and competencies required in the handling of OPAT include proper administration and exemption of IV medication. Also, thorough observation and treatment of potential complications and side effects of the medication, including allergic reactions e.g. anaphylaxis and infections, are requisite. Furthermore, the literature describes that nurses shall be thoroughly versed in the different IV accesses, equipment e.g. elastomeric pumps, and antibiotics (7, 54). Finally, some interview informants emphasise the importance of adequate pedagogical competencies which is required to inform and train patients in the handling of OPAT.

In the regional co-operation agreements, skills and competencies required in the handling of OPAT are outlined (for clarification see Appendix 5). However, the municipalities covered by the regional co-operation agreements have the responsibility of determining whether the municipal nurses have the outlined skills and competencies to manage OPAT. Moreover, municipalities are responsible for the training and competency development of municipal nurses, while hospitals are responsible for the training of hospital nurses. Though, some hospital departments provide courses in IV treatment that municipal nurses can attend, and some hospital departments offer municipal nurses assistance in concrete patient scenarios. The training and competency development of municipal and hospital nurses is partly comprised of courses in the handling of OPAT and pharmacology. Moreover, e-courses, e-learning programs, and digital informational materials are widely used across municipalities and hospital departments.

According to the literature review, patient self-administration requires, that patients or caregivers have received education in the administration of OPAT. Furthermore, patients and caregivers shall be trained in the administration of potential complications and side effects of the medication (2-4, 7, 57). The education might include thorough hands-on instructions by a registered and competent nurse (4). Similarly, in a Danish context, hospital nurses have the primary responsibility of providing self-administrated patients with sufficient training in OPAT prior to hospital discharge. Furthermore, the interview study reveals that self-administrated patients receive informational materials e.g. informational film clips regarding the handling of OPAT, which is in concordance with international recommendations (2, 54).

Part Two: Organisational challenges and possibilities and perspectives on future use of OPAT

G0008	Which organisational challenges and opportunities are attached to the use of OPAT?
Added question	Which organisational perspectives can be pointed out in relation to the future use and dissemination of OPAT?

This Domain describes organisational challenges and opportunities associated with use of OPAT. Moreover, it presents perspectives on future use and dissemination of OPAT in order to accommodate existing organisational challenges and ensure an optimised future use and dissemination of OPAT. The Domain is based on organisational challenges and opportunities identified by the interviewed physicians, nurses, municipal leaders

and regional/municipal staff employees and on the international experiences with use of OPAT identified in the systematic literature review.

Organisational challenges and opportunities

Challenges and opportunities concerning OPAT can be found at different levels. Challenges and opportunities are mentioned in the interviews at both organisational level, internal and external work processes, allocation of resources and practical challenges.

To begin with the latter, practical challenges are important challenges, which could easily be overlooked when planning an intervention like OPAT where treatment is transferred from hospital to the home environment or to an outpatient facility. These challenges have been identified both at hospital level and by the teams in the municipalities who are in charge of treating the OPAT patients in their homes or in outpatient facilities.

Starting at the hospital level, there is an indication in the interviews that some physicians might be reluctant to refer patients to OPAT if they are on a tight schedule because it is more time consuming to prepare patients for OPAT than to keep them at the hospital. There are several procedures to go through when preparing patients for OPAT which are avoided if patients are kept at the hospital. For example, the process of screening for eligibility for OPAT, getting hold of relatives, contacting the municipalities and so forth. A physician points out, that if you do not have many OPAT patients, it is a bit like starting from scratch every time. Also, a nurse from one of the hospitals, states that sometimes it is easier to keep the patients at the hospital, so referring patients to OPAT, is in many cases primarily for the sake of the patients.

OPAT patients in many cases also generate more work when it comes to registration. It has to do with the registration practice at the hospital, which in some cases prompts new registrations every day, because every infusion in the patients' home is considered a new contact. The workflow around OPAT patients is not completely alike at the different hospitals, but the health care professionals are sometimes challenged in meeting their treatment responsibility because OPAT patients are featured on separate records from the inpatients. Therefore, it can be a constant struggle to remember to follow up on the OPAT patients – as a physician says – 'out of sight, out of mind'. They wish for a secure and accessible system to handle OPAT patients and potential other patients treated in the homes. Another physician makes the point that sometimes attending to OPAT patients gives you the feeling that you have an extra ward to look after, because the beds at the hospital are quickly occupied by other patients.

There are also some practical challenges in accomplishing the OPAT work between hospital and the municipalities. If for example the municipality that a hospital collaborate with only provides OPAT treatment with a very specific selection of antibiotics or only are able to visit the patient's home two or three times a day, the number of patients eligible for OPAT are narrowed considerable. In addition, some municipalities do not take OPAT patients at all. A good collaboration with the hospital pharmacies is identified as part of the solution to some of these challenges. The pharmacies can help to identify treatment solutions best suited for treatment in the patients' homes matching the conditions in the municipalities and the patients' home.

It can be a challenge for the teams in the municipalities to get hold of relevant health care professionals at the hospitals, when they have questions considering the treatment plan or the actually performances of the treatment. In the interviews, the problem about planning and making a schedule for future work is also raised by the municipalities. There is often great variation over time in the number of OPAT patients in each municipality, which makes it difficult to figure out the optimal staffing level. OPAT patients in need of three or four visits a day also puts a lot of pressure on the municipality teams. For once, they have to visit the patient several times a day but they also have to wait at the patients' home during infusion. If they are delayed at another patient, it can be very difficult for them to make it in time for the next infusion.

The informants from the hospitals and the municipalities identify potential challenges around the collaboration on the OPAT patients. The accomplishment of an OPAT treatment involves multiple professionals, from multiple organisational units and the informants emphasise the need for coordination and communication to succeed. A physician emphasises that OPAT is reliant on everyone knows and follows the treatment plan. This can be challenged because there is often a large turnover in staff, both at the hospitals and in the municipalities, which increases the need to coordinate and communicate further. If the hospitals are responsible for training the teams in the municipalities it can be resources demanding, also considering the large turnover in staff.

Informants from both hospitals and municipalities mentions different financial challenges in the cooperation on OPAT patients. I could e.g. be the issue about hospitalised or ambulant patients. When a patient is referred to a OPAT, their status changes from hospitalised to ambulant, even though the ward still has considerable work around the patient.

Across the Danish hospitals and municipalities, the implementation of OPAT and the co-operation agreements is still in process. Therefore, the focus of the organisational opportunities of OPAT amongst respondents has been limited. Nevertheless, several interview informants point out that they can see the potentials of the treatment despite perceived barriers. One substantial organisational opportunity of OPAT is the fact that health professionals consider OPAT a highly meaningful task to carry out, since the treatment has immense value for patients. For instance, OPAT has shown to improve quality of life of those receiving OPAT (5, 6) (See Domain 4). In continuation hereof, the interview study reveals that one substantial precondition that should be present to ensure a decent OPAT service is that everyone involved are motivated and willing to carry out the service. So saying, the delivery of OPAT requires that everyone makes an effort.

Furthermore, government cost-cutting requirements involving the release of hospital beds are met, when patients are transferred to OPAT treatment, which also is considered an organisational opportunity of OPAT by the interview informants. An additional organisational opportunity pointed out by the informants is the fact that the release of hospital beds might result in the release of nursing resources, by which nurses can spend professional time on other nursing tasks. However, is not always the actual experience at the hospitals, as there can also be a large workload associated with the OPAT patients, as described above.

Another opportunity highlighted by the interview informants is the use of pumps in OPAT. By using e.g. an elastomeric pump the number of nurse visits in the patient's home or the patient's transportation to an outpatient clinic can be reduced significantly. Thus, the use of pumps can give patients a greater degree of independence and at the same time be resource-saving for hospitals and municipalities.

Finally, informants from the interview study express that OPAT forms the basis of a close cross-sectional cooperation between hospitals, municipalities, and general practitioners, which provides a breeding ground for professional back-and-forth along with a good insight into each other's professional fields and competencies.

Future improvements and potentials

The interview informants have various suggestions on how OPAT can be further developed and disseminated, as well as future potentials for relocating other types of treatment from the hospital into the patient's home or local care facilities.

Across hospitals and municipalities, the informants point out that there is a great potential for transferring more treatment outside the hospital. Parenteral nutrition, blood transfusions and fluids are relevant examples. This is partly due to the fact that many municipalities have upgraded their capacity and competencies the recent years. As a result, the municipalities can take care of patients with far greater health care needs than before.

It is also mentioned that a large proportion of patients is estimated to have the resources to complete treatment outside the hospital. However, according to the interview informants, this requires that the hospitals are willing to delegate a greater part of the responsibility for the patient (while retaining the overall medical treatment responsibility). In addition, it is suggested to consider the involvement of the general practitioners, if treatment increasingly is transferred from the hospital to the primary care sector. Some of the municipalities in the interview study, which are currently not financially compensated for the delivery of OPAT, emphasize that it requires a formal payment and settlement system between region and municipality if they are to receive OPAT (and other) patients to a greater extent.

In general, informants from the municipalities wish that a specific co-operation agreement on OPAT will be drawn up in the regions where it does not currently exist. For example, a formalized division of roles and responsibilities as well as clarity about whether it is an optional task to handle OPAT in the municipalities is requested. Furthermore, an informant expresses that a national agreement could be beneficial so that OPAT is organised equally across regions. Another informant suggests that the cross-sectoral task force that developed the co-operation agreement is maintained when the agreement is implemented, in order for the task force to continue the development and improvement of OPAT.

The importance to focus on the working environment for the visiting nurses, is mentioned as a further potential for improvement. It is often necessary for them to carry heavy equipment and they spend a large amount of time on driving and documentation in OPAT trajectories, which minimizes the time for other tasks. In this context, the possibility of using pumps in OPAT to a greater extent is pointed out by the informants as a potential for improvement, as it can ease the workload for the nurses.

Finally, both hospitals and municipalities request integrated centres at the hospitals that specialise in IV treatment, which can be compared with the OPAT clinics described in the international literature (3-7). The centres must be staffed with competent health care professionals, including physicians specialising in e.g. infectious diseases. The centres can form a coordinating unit and be responsible for communication with external partners such as municipalities. The medical treatment responsibility remains with the referring departments. It will provide a boost of competence internally at the hospitals, because the IV centres will generate experts in the field over time. Moreover, the municipalities know where they can turn if they have questions or need advice on IV treatment. This may partly correspond to the clinics established at e.g. Odense University Hospital (described in 'OPAT delivery models'), but according to the interview study, actual IV centres are not a widespread organisation in Danish hospitals. Economy is highlighted as a barrier to organising such centres, as it requires significant resources to establish them.

As described above, special outgoing teams or discharge teams are used in OPAT at some hospitals. According to the interview informants, it minimizes the risk of adverse events that the referral and coordination of OPAT patients is handled by a specialized team. This can support the international recommendations on specific OPAT teams (2-6, 54-56, 58).

7.4 Discussion and conclusion

Some methodological challenges in the organisational analysis should be taken into account. First, the studies from the literature are mainly descriptive. They provide insight into how OPAT can be organised, but only to a limited extend are the organisational consequences of OPAT assessed. Perspectives on consequences included in the organisational analysis are based on qualitative interviews with health professionals involved in the delivery of OPAT and thus on subjective experiences and perceptions rather than objective quality and performance measurements. As such, there is a need for future research that systematically integrate analysis of organisational aspects with more objective quality and performance indicators, e.g. resource consumption,

patient safety and quality in treatment, to substantiate conclusions on optimised use of OPAT. Second, the geographical context of the included studies should be taken into consideration in relation to the transferability and generalisability of the results of these studies to a Danish context. This, due to the fact that organisation of and processes within health care systems differ across national contexts and thus potentially also in relation to the delivery of OPAT. However, several of the recommendations from the literature review have been re-discovered in the interview study, emphasizing the validity of these results. Third, all hospital departments and municipalities involved in the delivery of OPAT have not been included in the interview study. Thus, the organisational analysis does not provide a complete picture of the delivery of OPAT and associated challenges and opportunities in Denmark. However, the interview study is based on a relatively large sample with representatives from both different regions, hospitals, municipalities, specialties and professional background, all with experience with OPAT, and data saturation was regularly discussed during data collection. In a future perspective, the local experience gathering in some of the regions will provide an in-depth insight into the organisation of OPAT in a Danish context.

Despite these outlined challenges the organisational analysis forms a substantial contribution to a description of the organisational aspects associated with the delivery of OPAT in a Danish context. Furthermore, the organisational analysis provides a first step towards establishing relevant knowledge about challenges and opportunities associated with the delivery of OPAT to support an optimised future use and dissemination of OPAT.

The results of the analysis of the organisational aspects of OPAT shows that the organisation of OPAT varies in Denmark but also internationally. In a Danish context, there are three general delivery models of OPAT, defining the type of administration and the treatment arena. These include home-administration managed by municipalities, self-administration managed by hospitals and treatment in local care facilities managed by either municipalities or hospitals. In the health economic domain, these models are further elaborated with a description of a number of different and more detailed course of treatments. Compared to the international organisation of OPAT, the field is less specialized in Denmark. For instance, some international health care organisations operate with particular OPAT clinics and specialized OPAT teams who manage the OPAT treatment across departments at the hospital. Despite variation in the organisation of OPAT in Denmark, visitation, preparation, follow up, and completion of patient continuity of care generally occur alike in the five regions. However, the application of different kinds of pumps, self-administration, the delivery of medicine, and the practice of registration is not homogeneously performed currently. The interview study shows that OPAT in an ambulant hospital clinic is used to a very limited extent in the hospitals included in the interview study. If ambulant treatment is to be disseminated in a Danish context, there is a need to develop and establish the necessary medical equipment and facilities. This is seen in some hospitals with specific ambulant clinics where IV treatment can be provided.

In Denmark, some regions and municipalities have established a co-operation agreement that defines the essential structures and divisions of responsibilities in relation to OPAT. The regional co-operation agreements have shown to be of great importance in working with OPAT across sectors. In those regions, where no concrete co-operation agreement concerning OPAT is available, there is a great wish for an agreement that formalizes the cross-sectoral co-operation. According to the international literature, a successful implementation of OPAT requires that the nurses involved have the right competencies to perform the treatment. Within the regional co-operation agreements and the national clinical guidelines, a framework of training and competency development amongst nurses managing OPAT is included. For instance, it appears which competences involved nurses are expected to have to manage OPAT. The perceived need of training and competency development amongst municipal nurses, however, varies. A clear division of responsibilities is also an essential precondition for OPAT to function. In the co-operation agreements, delegation of responsibilities is described.

There can be different divisions of labour internally at the hospitals and in the municipalities in relation to OPAT treatment. However, there is a general agreement about the delegation of responsibilities (e.g. the medical treatment responsibility) between regions and municipalities, in cases where municipalities are involved.

The organisational analysis further shows that OPAT is associated with both organisational challenges and opportunities. According to the interview informants, challenges regarding OPAT include e.g. an increased burden of labour especially in the preliminary phase of OPAT and in the continuous monitoring of patients. Furthermore, some municipalities only have limited resources to manage OPAT care trajectories due to the fact that it is a comprehensive task for nurses to visit patients 3-4 times a day. Moreover, coordination and communication is an important precondition for OPAT, however, it can give rise to certain challenges, because of the involvement of many health professionals. According to the interview informants, organisational opportunities include the fact that OPAT is a highly meaningful task to manage for the involved health professionals, because patients appreciate to continue treatment at home familiar surroundings. Furthermore, with OPAT, nursing resources at the hospital can be freed, and the cross-sectional co-operation between involved professionals is strengthened. Thus, a consensus amongst the interview informants of whether OPAT is resource-demanding or resource saving lacks. As regards potentials, the interview informants see great potential in moving more types of treatment from the hospital to patients' homes or in the community, for instance, nutrition, blood transfusion, and fluids. Moreover, potentials are seen in the application of pumps, which can optimize the treatment, and more specialised centres at the hospitals, that manage IV treatment, as seen in other countries and in some hospitals in Denmark. This can potentially give the area of OPAT a competency boost as treatment will be concentrated on fewer hands with particular insight and experience in the field of infectious diseases.

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8 COSTS AND ECONOMIC EVALUATION (ECO)

8.1 Research questions

ID	Research question
E0009	What were the measured and/or estimated costs of Outpatient Parenteral Antibiotic Therapy and Inpatient Parenteral Antibiotic Therapy (resource use valuation)?
E0005	What is (are) the measured and/or estimated health-related outcome(s) of Outpatient Parenteral Antibiotic Therapy and Inpatient Parenteral Antibiotic Therapy (outcome identification, measurement and valuation)?
E0006	What are the estimated differences in costs and outcomes between Outpatient Parenteral Antibiotic Therapy and Inpatient Parenteral Antibiotic Therapy?
E0010	What are the uncertainties surrounding the costs and economic evaluation(s) of Outpatient Parenteral Antibiotic Therapy and Inpatient Parenteral Antibiotic Therapy?
E0012	To what extent can the estimates of costs, outcomes or economic evaluation(s) be considered as providing valid descriptions of differences between Outpatient Parenteral Antibiotic Therapy and Inpatient Parenteral Antibiotic Therapy?
E0013	What methodological assumptions were made in relation to investigating economic evaluation of Outpatient Parenteral Antibiotic Therapy and Inpatient Parenteral Antibiotic Therapy?

Outpatient parenteral antibiotic therapy (OPAT) is widely used in most developed countries, providing considerable opportunities for improved patient centered care and potential cost savings. However, it is implemented only partially in Denmark, using a variety of different models of care.

8.2 Objective

The objective of the health economic domain was:

- To evaluate evidence of the cost-effectiveness of OPAT models
- To assess the costs of different care models for the delivery of OPAT in Denmark

The economic domain consists of three complimentary elements; a systematic literature review (8.3), a micro-costing analysis of different care models in a Danish setting (8.4), and important considerations regarding the implementation of OPAT (8.5). The first two elements will be presented as two individual studies with separate methods, results and discussion sections. The third element presents important considerations, emerged through the conduct of the micro-costing analysis that are of relevance to decision-makers in a Danish setting. A joint conclusion is presented in the end of the Domain.

8.3 Systematic literature review

Methods

A total of 503 articles were identified through the joint literature search strategy and were assessed for eligibility for inclusion in the literature review of the economic domain. The economic review included evaluations of costs and cost-effectiveness of OPAT in relation to IPAT. The review included randomized controlled trials, observational studies, prospective and retrospective studies, simulation based evaluations and systematic reviews. The review did not focus on any selected age group or condition, thus including children as well as

adults and all kinds of diagnoses. For study design, analyses of cost-effectiveness, cost-utility, cost-minimization and cost-consequence were considered.

Types of interventions

The intervention was OPAT, which was defined as a service that prevents the need for hospital admission. All different OPAT services were of interest in the review, and therefore we included all studies evaluating different OPAT delivery models. The OPAT treatment was limited to include only intravenous treatments.

Outcome measures

Included outcome measures were (see domain 4, EFF): 1. Mortality: Any mortality in outpatient/inpatient groups, 2. Morbidity: Four morbidity outcomes are reported: treatment failure, resolution of infection, lung function and clinical success, 3. Readmission: Any readmission after discharge. Follow-up are specified in some studies, 4. Quality of life, and 5. Satisfaction.

Additionally, health utilities or Quality Adjusted Life Years (QALY) were included as outcome measures from the health economic literature.

Eligibility criteria

The exclusion criteria included: Economic evaluations of a specific antibiotic agent, OPAT studies with focus on oral or intra-muscular treatments, patient populations with characteristics that differed significantly from the general population (e.g. homeless population), publication types: case reports/case series/study protocols/conference abstracts/PhD reports, non-English language, non-peer-reviewed journals, and no full text available.

Selection of studies

The articles retrieved by the electronic searches were assessed first through a title/abstract screening by two authors. Full-text papers were retrieved for all potentially eligible studies identified and two individual members of the project group independently assessed their eligibility. Studies were selected according to pre-specified inclusion criteria and disagreements resolved by discussion.

Quality assessment

The methodological quality of systematic reviews was assessed using the AMSTAR checklist (73). This critical appraisal tool consists of 16 items to take account of flaws in critical domains, which may greatly weaken the confidence that can be placed in a systematic review. The critical domains considered are; Protocol registered before commencement of the review, adequacy of the literature search, justification for excluding individual studies, risk of bias from individual studies being included in the review, appropriateness of meta-analytical methods, consideration of risk of bias when interpreting the results of the review, and assessment of presence and likely impact of publication bias. The tool rates the quality of the review into one of 4 categories; High, Moderate, Low, Critically low expressing the overall confidence in the results of the review.

The quality of the economic analyses was assessed using the Drummond checklist (74). This tool assigns a score according to the following ten parameters: definition of research question, description of adequate alternatives, evidence of effectiveness, relevance of the costs and consequences, credibility of the value of costs and consequences, temporal adjustment of the costs and consequences, analysis of incremental cost and consequences of the alternatives, sensitivity analysis, and adequate discussion.

Classification of the quality assessment was considered high for studies ranging from 8-10, high medium for studies ranging from 6 to 7, low medium for studies with scores ranging from 4 to 5, and low for studies below 4.

Data extraction

The reviewers conducted the data extraction. The following variables were analysed: country, year of publication, year of cost-analysis, currency, type of perspective of the cost-analysis, target population, OPAT strategy applied, conditions treated, costs, incremental analyses, and sensitivity analysis.

The average cost and treatment duration of both OPAT strategy and IPAT strategy were extracted. For studies that did not provide these results, estimates were made based on the available data. Treatment duration and cost per episode for OPAT and IPAT were used to calculate the incremental cost per day. To compare results across different diagnoses and treatment durations, incremental cost per day was considered the primary result for the analyses. The incremental cost was related to the IPAT cost and calculated as percentage OPAT savings.

In order to summarise and compare cost results, we converted all cost estimates into EUR and inflated the costs to 2019 prices based on the year of the cost analysis performed in each study. In articles where costing year were not explicitly stated, we assumed costing year to be the final year in which the study was conducted.

We also analysed the incremental cost for relevant subgroups. The subgroups were different location of study, age of population, different conditions treated, study design, OPAT delivery models, and quality assessment (Drummond's checklist scores).

Data were analysed using STATA version 16.

8.3.2 Results

We obtained 503 studies from the electronic search after the common title/abstract screening. Of these studies 81 full-text articles were assessed for eligibility. In total 28 articles were included, of which 7 were systematic reviews and 21 were original studies.

Description of included reviews

The characteristics of the 7 included reviews are summarised in Appendix 7.

All included review articles ran searches from the inception of the electronic databases. One review ran searches to 2014 (24), two until 2015 (22, 75), one until 2016 (76) and three until 2017 (25, 77, 78). The reviews were published between 2015 and 2019. In one review, searches were limited to RCT design (76), one included RCT studies as well as quasi-randomised controlled studies (75), one included all study types except for single case reports (22), one included all studies reporting original data (24), one included economic evaluations (25), and in two cases all study types were included (77, 78).

The aim of the reviews varied. Two reviews aimed to perform an economic comparison of OPAT versus IPAT (25, 78) and five reviews aimed at describing effectiveness as well as costs of OPAT compared to IPAT (22, 24, 75-77). Regarding the OPAT comparator, four reviews were focused at delivery of intravenous treatment in the patient's home (24, 75-77), two reviews were considering different OPAT delivery models (22, 25), and one review did not describe the details of the OPAT comparator (78). Three of the reviews included an adult population (22, 76, 78), one included only children (77), and three included both (24, 25, 75). Regarding diagnoses of the included patient population, one review included acute infections (77), one included cystic fibrosis (75) and five included multiple diagnoses (22, 24, 25, 76, 78).

The quality of the reviews was evaluated using the AMSTAR checklist. One review was found to be of critically low quality (78), five of moderate quality (22, 24, 25, 75, 77), and one were found to be a high quality review (76).

Costs in the included reviews

The number of included studies in the reviews that provided data for the cost comparison/analyses varied, and there was an overlap of some studies that were included in several of the reviews (see Appendix 6). In total 65 studies were included across reviews, which covered the period from 1978 to 2017.

The reporting of the cost analysis varied between the reviews. The review by Balaguer & Gonzalez de Dios reported the cost per day of OPAT (15.08 AUS $) and IPAT (23.77 AUS $) from the included studies (cost difference -8.69 AUS $). The authors stated that it was difficult to draw any conclusions for practice on the basis of the review, and that further research was needed (75).

The review by Polinski et al. reported either cost and cost difference results per day and/or episode in USD from the individual studies included, with cost differences per day ranging from -9 USD to -179 USD per day. The authors concluded that the costs associated with home infusion were consistently, significantly lower than hospitalisation, however; they state that the quality and costs of the included studies merits additional research (24).

The review by Bryant & Katz reported the cost and cost difference results per episode of the five included studies in USD. The included studies all showed treatment to be cost saving at home compared to hospital

with cost differences per episode ranging from -1348 USD to -8756 USD, implying savings of 30-75%, regardless of whether home-based treatment was administered by families or nursing staff. They concluded that the benefits of home-based antibiotics costs are clear (77).

The review by Shepperd et al. was not able to combine cost data due to the different ways costs had been calculated in the included studies. Instead, they reported the cost and cost differences per day or episode of the included studies in the original currencies of the individual study. The analysis was performed for different subgroup of patient populations (elderly with medical condition, recovery from stroke and COPD and community-acquired pneumonia). They concluded that hospital at home may decrease treatment costs slightly when compared with hospital admission, but that caregiver costs may offset this difference. They advise future research to include a formal, planned economic analysis including costs that are sensitive to the different resources used during a treatment episode (76).

The review by Mitchell et al. evaluated the cost-effectiveness of OPAT compared to IPAT and concluded that OPAT overall was more cost-effective than inpatient care (22).

The review by Boese et al. calculated therapy costs into cost per day in EURO to allow for better comparison of studies. Costs per day ranged from 28€ to 269€ for OPAT and from 110€ to 1125€ for IPAT. The mean cost ratio between OPAT and IPAT costs was 4.8 (1.1-17.3) per day. They concluded that the assumption of cost reduction with OPAT seems reasonable (78).

Finally, the review by Psaltidikis et al. compared the average cost of OPAT treatment to that of hospitalisation as well as percentage OPAT cost savings. Considering all 35 included studies, the general average economic savings per OPAT episode was 57.19% (from -13.03% to 95.47%). Analyses of the six included comparative studies only showed average economic savings of 16.93% (from -13.03% to 46.86%), which was lower than the non-comparative studies. For each included OPAT strategy the average savings were as follows: 61.93% (from 18.34% to 95.47%) for self or carer administration; 57.46% (from-13.03% to 92.22%) for home health nursing; 57.27% (from 11.05% to 90.40%) for infusion centres; 56.12% (from 10.31% to 83.88%) for combined strategy at home (i.e. self, caregiver and health nursing administration); and 52.93% (from -2.68% to 86.62%) for combined strategies (infusion centres and home administration). The authors concluded that OPAT appears to be good value for money, as most included studies indicated that OPAT was a cost-saving strategy compared to hospitalisation (25).

Description of included original studies

The characteristics of the 21 included original studies are summarised in Appendix 8. 11 of the included studies were previously included in some of the reviews (see Appendix 6).

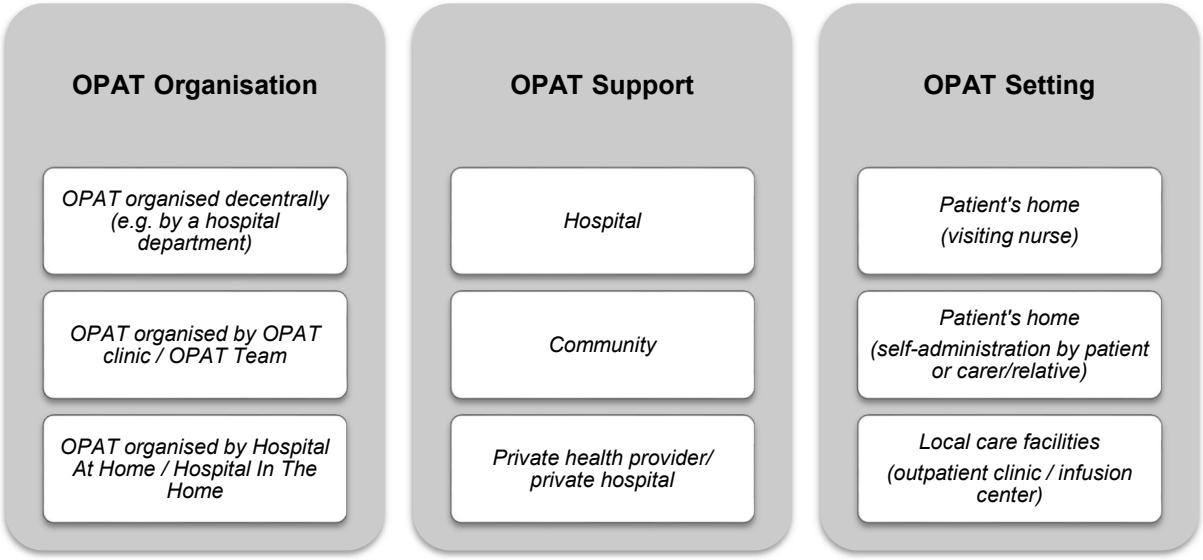
There was considerable inter-country heterogeneity among the original studies, covering 11 countries. Overall, six (29%) studies were from North America (29, 79-83), seven (33%) studies were from Europe (30, 33, 84-88), five (24%) studies were from Oceania (34, 40, 85, 89, 90), two (10%) studies were from Asia (91, 92), and one study (5%) was from Latin America (93). The number of studies within each category is listed in Table 8.

With regard to the study design, two studies (10%) were economic evaluations based on randomised controlled trials (29, 40), 19 studies (90%) were observational whereof 12 were retrospective (63%) (79-81, 84-92), four prospective (21%) (30, 33, 34, 94), and three model-based (14%) (82, 83, 93). 12 of the included original studies (57%) performed comparative analyses involving hospitalized patients (29, 30, 33, 34, 40, 82, 83, 85-87, 89, 91) and nine studies (43%) generated hypothetical IPAT estimates for the cost comparison (79-81, 84, 88, 90, 92-94).

Different populations were evaluated; 14 studies (67%) included adult population (30, 79-82, 84-88, 90, 91, 93, 94), four (19%) included children (34, 40, 83, 89) and three included both (14%) (29, 33, 92). There was great heterogeneity regarding conditions treated in the studies; seven studies (33%) included multiple diagnoses (80, 81, 84, 88, 89, 92, 93), three (14%) included cellulitis (34, 40, 85), three (14%) febrile neutropenia (cancer) (29, 82, 83), two (10%) infectious endocarditis (86, 87), and there was only one study (5%) in each of the following conditions; acute pyelonephritis (91), uncomplicated diverticulitis (30), cystic fibrosis (33), Acute Dental Infections (ADI) (94), diabetic foot infection (90) and community-acquired pneumonia (CAP) (79).

The OPAT regimens were provided via different organisational models and in order to analyse the potential differences in costs related to the OPAT delivery, we created a 3-level model for OPAT delivery based on the Danish organisational model (see Figure 7). **OPAT organisation** referred to how the OPAT service was organised and was divided into three categories: 1. *OPAT organised decentrally,* where the OPAT service was decentrally run by e.g. the treating hospital departments, 2. *OPAT organised by OPAT clinic or OPAT Team,* where the OPAT service was run from a centralised OPAT clinic or a multidisciplinary OPAT Team in the hospital or municipality, and 3. *OPAT organised by Hospital at Home/Hospital-in-The-Home*, which are hospital-based units that seek to shorten the usual hospital admission by providing a wide list of services hereunder OPAT. **OPAT support** referred to which organisation that provided the support during the OPAT treatment and was divided into three categories: 1. *Hospital*, where the visiting nurse or staff providing other supportive services was employed by the hospital, and 2. *Community*, where the supportive staff e.g. district nurse was employed by the community or municipality, and 3. *Private health provider/private hospital,* where the support was delivered by a private organisation. **OPAT setting** referred to where the OPAT treatment was received and was divided into: 1. *Patient's home* – nurse-administered treatment by a visiting nurse, 2. *Patient's home* – with self-administered treatment by the patient or a carer/relative, and 3. *Local care facilities*, where the patient visited an outpatient clinic or infusion centre to receive the treatment.

Figure 7: 3-level organisational model to analyse different OPAT delivery



In the 21 included studies OPAT organised decentrally was investigated in nine studies (43%) (29, 30, 33, 82, 83, 86, 88, 90, 91), six studies (29%) assessed OPAT organised from a centralised OPAT clinic or an multidisciplinary OPAT Team (79-81, 92-94), and OPAT delivered by Hospital at Home/In the Home was present in six studies (29%) (34, 40, 84, 85, 87, 89). The OPAT support and outpatient visits were in 16 of the studies (76%) delivered by the hospital (30, 33, 34, 40, 80-87, 89, 91-93), in three studies (14%) the OPAT support

was community-based (29, 90, 94) and in two studies (10%) the OPAT support was delivered by a private supplier/hospital (79, 88). In 17 studies (81%) patients were treated in their home environment, whereof OPAT was nurse-administered in 16 studies (29, 30, 34, 40, 81-91, 94) and self- administered in only one study (33). In four studies (19%) the patient received OPAT treatment in an outpatient clinic or infusion centre (79, 80, 92, 93).

The quality of the included studies was evaluated using Drummond's checklist (Appendix 9) and was subsequently divided into four categories; high, high medium, low medium, and low. Of the included studies, five were (24 %) found to be of high, high medium, and low medium quality respectively. Six studies (29%) were found to be of low quality.

Table 8: Categories of included studies

Category		Number of studies (%)
Country		
	North America	6 (29)
	Europe	7 (33)
	Oceania	5 (24)
	Asia	2 (10)
	Latin America	1 (5)
Study design		
	Randomised controlled trial	2 (10)
	Retrospective	12 (57)
	Prospective	4 (19)
	Model-based	3 (14)
Study type		
	Comparative	12 (57)
	Hypothetical IPAT	9 (43)
Population		
	Children	4 (19)
	Adults	14 (67)
	Adults and children	3 (14)
Disease condition		
	Multiple diagnoses	7 (33)
	Cellulitis	3 (14)
	Febrile neutropenia (cancer)	3 (14)
	Infectious endocarditis	2 (10)
	Acute pyelonephritis	1 (5)
	Uncomplicated diverticulitis	1 (5)
	Cystic fibrosis	1 (5)
	Acute Dental Infections	1 (5)
	Diabetic foot infection	1 (5)
	Community-acquired pneumonia	1 (5)
OPAT Organisation		
	OPAT organised decentrally	9 (43)
	OPAT clinic/OPAT Team	6 (29)
	Hospital at Home OPAT	6 (29)
OPAT setting		
	Patient's home	17 (81)
	Outpatient clinic or infusion centre	4 (19)
OPAT Support		

Category		Number of studies (%)
	Hospital	16 (76)
	Community	3 (14)
	Private health provider/ hospital	2 (10)
Costing perspective		
	Hospital	13 (62)
	Health care system	8 (38)

Costs in the original studies

The costing perspective and thereby included costing categories differed among the included studies. 13 studies (62%) applied a hospital perspective (30, 33, 34, 40, 79, 81, 84-87, 89, 91, 92) and eight studies (38%) used a health care system perspective (29, 80, 82, 83, 88, 90, 93, 94). Costing information was incomplete in nine studies (43%) (30, 33, 79, 87-89, 91, 92, 94), where we were unable to assess the included costing categories. 12 studies (57%) described their costing strategy (29, 34, 40, 80-86, 93), and included relevant costs as set-up costs, staff wages, drugs, equipment, consumables, transportation and overheads.

The studies generally included direct costs of OPAT in the analyses. However, the inpatient group (comparator) was not evaluated directly in nine studies (43%). In these studies, hospitalization costs, such as parameters related to the antibiotic treatment (i.e. duration, drug, and venous access) and hospitalization days, were estimated based on the assumption that the same number of OPAT days should be accounted for in the hypothetical comparator group.

Considering all 21 studies, the general average cost difference per OPAT day was 548.11€ (ranging from -31.77€ to -1861.64€ per day) corresponding to a mean cost saving of 59% and a mean ratio of 2.44 (table 9). The results indicate a relevant reduction compared to inpatient antibiotic therapy. Considering only the 12 comparative studies, the mean savings per OPAT day was -490,09€ (ranging from -71.76€ to -1.092,11€ per day) corresponding to a mean cost saving of 49%, which was less than the mean cost savings per day in studies with hypothetical comparator, where it was 625.48€ per OPAT day (ranging from -31.77€ to -1861.64€ per day) corresponding to a cost reduction of 76%.

Table 9: Cost difference per day (2019 - €), cost ratio and cost savings (%) from the included studies

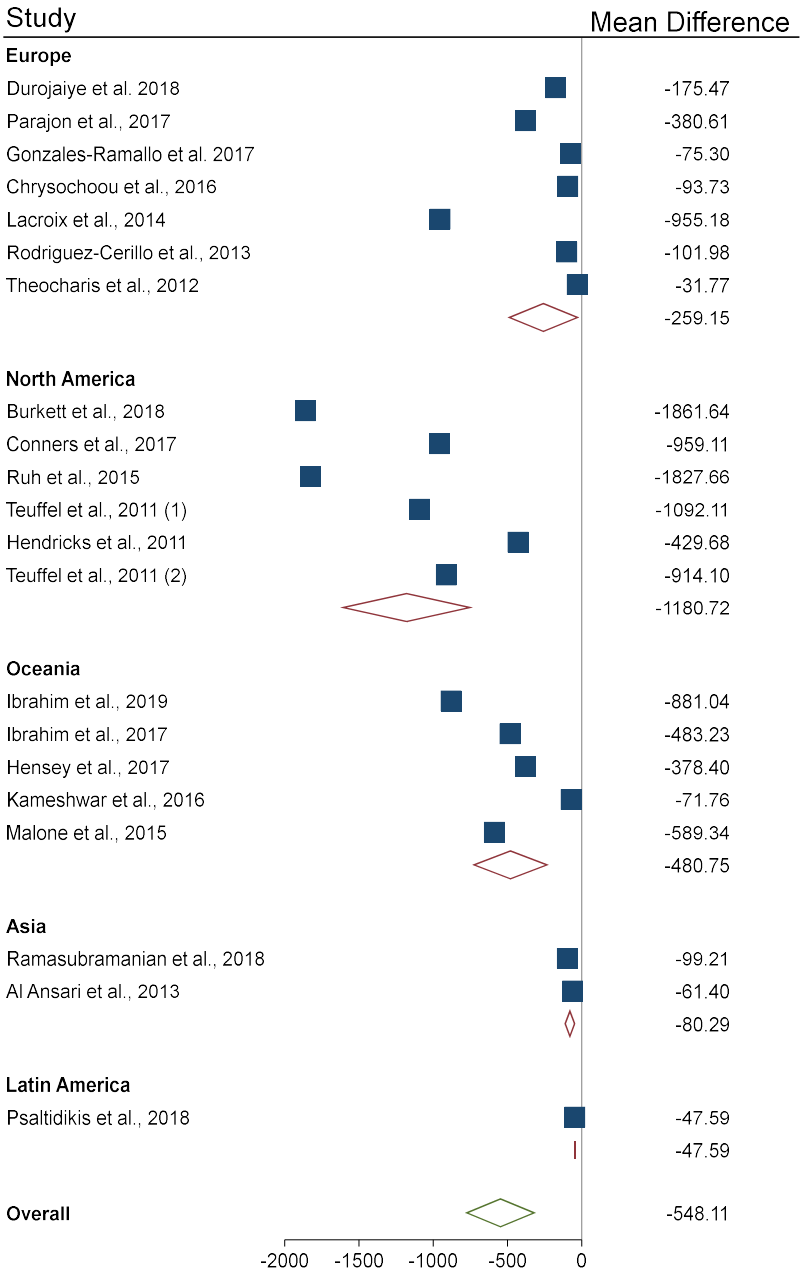
Study	Year	OPAT Organisation	*OPAT Support*	*OPAT Setting*	Cost per day OPAT (€)	Cost per day IPAT (€)	Cost difference per day (€)	Cost ratio (OPAT/ IPAT)	Cost savings (OPAT/ IPAT)
Hendricks et al.	2011	OPAT organised decentrally	Community	Patient's home (visiting nurse)	1.455	1.884	-430	1,30	23%
Teuffel et al. (2)	2011	OPAT organised decentrally	Hospital	Patient's home (visiting nurse)	751	1.665	-914	2,22	55%
Teuffel et al. (1)	2011	OPAT organised decentrally	Hospital	Patient's home (visiting nurse)	684	1.776	-1.092	2,60	62%
Theocharis et al.	2012	OPAT organised decentrally	Private	Patient's home (visiting nurse)	184	216	-32	1,17	15%
Rodriguez-Cerillo et al.	2013	OPAT organised decentrally	Hospital	Patient's home (visiting nurse)	437	539	-102	1,23	19%

Study	Year	OPAT Organisation	*OPAT Support*	*OPAT Setting*	Cost per day OPAT (€)	Cost per day IPAT (€)	Cost difference per day (€)	Cost ratio (OPAT/ IPAT)	Cost savings (OPAT/ IPAT)
Al Ansari et al.	2013	OPAT Clinic/Team	Hospital	Outpatient clinic/infusion centre	41	102	-61	2,50	60%
Lacroix et al.	2014	OPAT organised decentrally	Hospital	Patient's home (visiting nurse)	243	1.198	-955	4,93	80%
Malone et al.	2015	OPAT organised decentrally	Community	Patient's home (visiting nurse)	161	750	-589	4,66	79%
Ruh et al.	2015	OPAT Clinic/Team	Hospital	Patient's home (visiting nurse)	265	2.093	-1.828	7,89	87%
Kameshwar et al.	2016	Hospital at Home/In the Home	Hospital	Patient's home (visiting nurse)	498	570	-72	1,14	13%
Chryso-choou et al.	2016	OPAT organised decentrally	Hospital	Patient's home (self-administration)	156	250	-94	1,60	38%
Conners et al.	2017	OPAT Clinic/Team	Community	Patient's home (visiting nurse)	193	1.152	-959	5,98	83%
Hensey et al.	2017	Hospital at Home/In the Home	Hospital	Patient's home (visiting nurse)	135	513	-378	3,81	74%
Parajon et al.	2017	Hospital at Home/In the Home	Hospital	Patient's home (visiting nurse)	782	1.163	-381	1,49	33%
Gonzales-Ramallo et al.	2017	Hospital at Home/In the Home	Hospital	Patient's home (visiting nurse)	470	546	-75	1,16	14%
Ibrahim et al.	2017	Hospital at Home/In the Home	Hospital	Patient's home (visiting nurse)	334	817	-483	2,45	59%
Rama-subrama-nian et al.	2018	OPAT organised decentrally	Hospital	Patient's home (visiting nurse)	164	263	-99	1,60	38%
Psaltidikis et al.	2018	OPAT Clinic/Team	Hospital	Outpatient clinic/infusion centre	132	179	-48	1,36	27%
Burkett et al.	2018	OPAT Clinic/Team	Private	Outpatient clinic/infusion centre	177	2.039	-1.862	11,51	91%
Durojaiye et al.	2018	OPAT Clinic/Team	Hospital	Outpatient clinic/infusion centre	113	288	-175	2,56	61%
Ibrahim et al.	2019	Hospital at Home/In the Home	Hospital	Patient's home (visiting nurse)	601	1.482	-881	2,47	59%
Mean					380	928	-548	2,44	59%

Looking into the level of costing information, the mean cost savings in the studies supplying sufficient information was -628.54€ (57%) (-47.59€ to -1827.66€), and in studies with incomplete costing information the mean savings were -440.87€ (64%) (-31.77€ to -1861.64€).

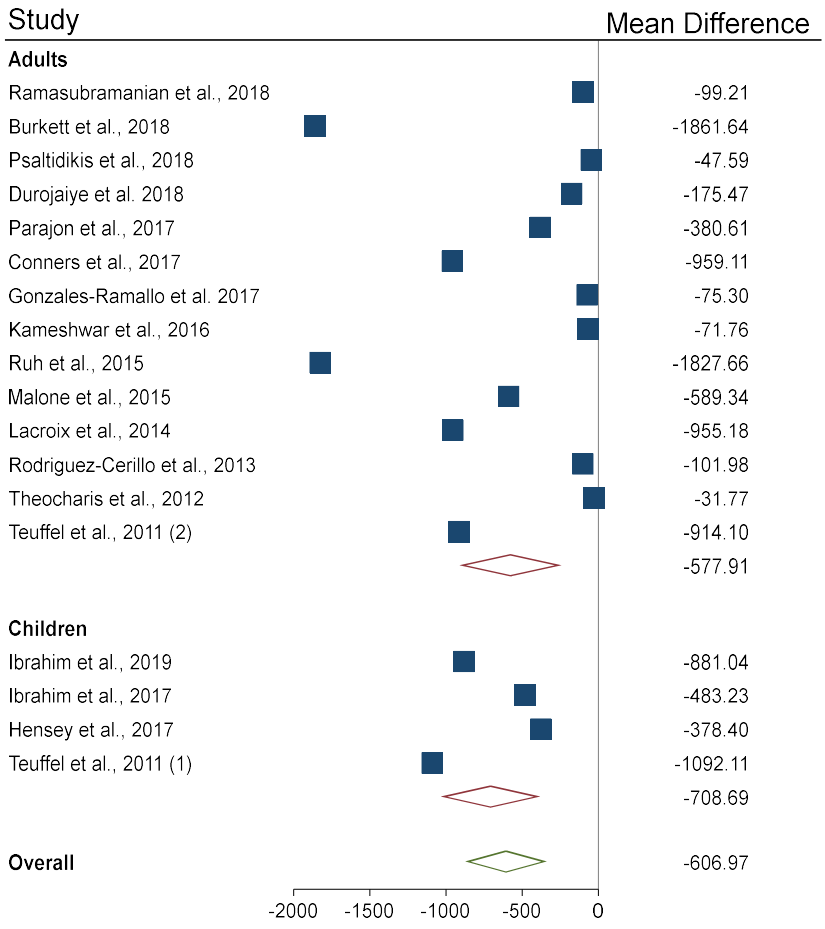
Divided into the different continents, mean savings were estimated as follows (see Figure 8): Europe -259.15€ (43%) (-31.77€ to -955.18€), North America -1180.72€ (67%) (-429.68€ to -1861.64€), Oceania -480.75€ (58%) (-71.76€ to -881.04€), Asia -80.30€ (44%) (-61.40€ to -99.21€), and Latin America -47.59€ corresponding to a cost saving of 27% (only one study).

Figure 8: Cost difference (2019 - €) per OPAT day divided into continents and sorted by publication year.



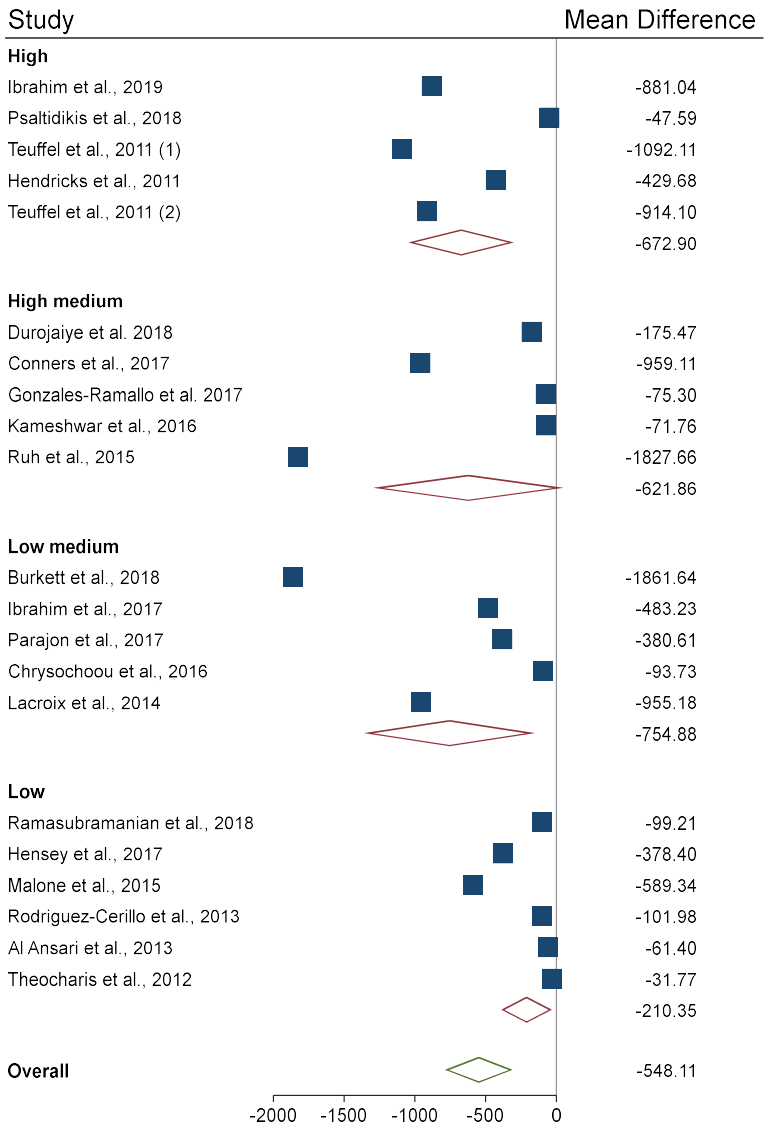
The mean savings per day related to different age of the patient population was 577.91€ (67%) for adults and 708.69€ (62%) for children, however, according to the forest plot no systematic differences related to age was seen (see Figure 9). Systematic differences in cost differences related to treatment of the different diagnoses were also not detected.

Figure 9: Cost difference (2019 - €) per OPAT day divided by patient age and sorted by publication year.



Regarding the quality of the studies (Appendix 9), it appeared that studies of low quality generally found slightly smaller cost savings per OPAT day (average savings of 53%) compared to studies in the other quality categories (average savings of 60%) (see Figure 9). This tendency was persistent also when Asian and Latin American studies, that showed the smallest cost savings (Figure 10), were excluded.

Figure 10: Cost difference (2019 - €) per OPAT day divided by quality category and sorted by publication year.

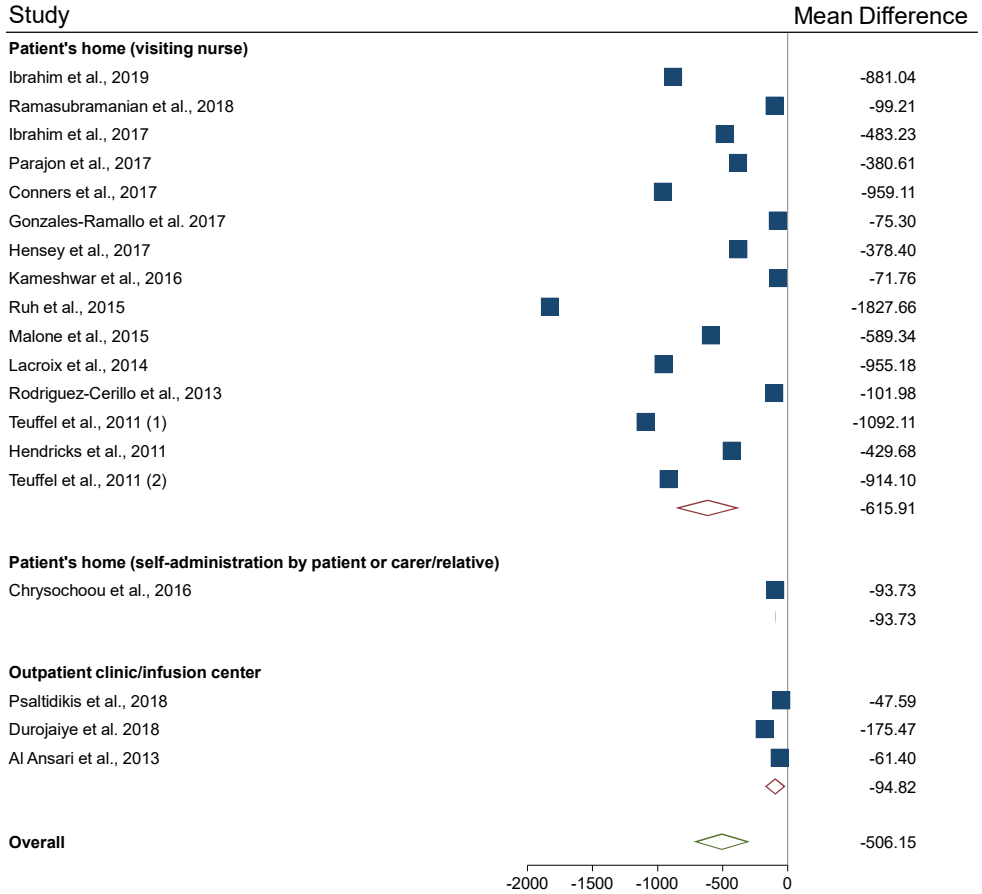


Considering the different OPAT organisational models, OPAT organised decentrally showed mean savings of 468.53€ (50%) per OPAT day (ranging from -31.77€ to -1001.76€ per day), OPAT organised by an OPAT clinic or a OPAT Team showed mean savings of 822.15€ (84%) per OPAT day (ranging from -47.59€ to -1861.64€ per day), and OPAT organised through Hospital at Home/In the Home showed mean savings of 378.39€ (45%) per OPAT day (ranging from -71.76€ to -881.04€ per day). Considering only European studies the delivery models showed following savings compared to IPAT: OPAT organised decentrally 54%, OPAT clinic or an OPAT team 61%, and OPAT organised through Hospital at Home/In the Home 27%. Regarding OPAT support, support by the hospital showed mean savings of 471.78€ (57%) per OPAT day (ranging from -47.59€ to -1827.66€), community-based support showed mean savings of 659.38€ (52%) per OPAT day (ranging from -429.68€ to -959.11€ per day). OPAT organised and delivered by a private health provider or hospital showed mean savings of 946.71€ (84%) per OPAT day (ranging from -31.77€ to -1861.64€ per day) (only two studies).

Considering the OPAT setting, OPAT at home (nurse-administered) showed mean savings of 579.40€ (56%) per OPAT day (ranging from -31.77€ to -1827.66€ per day), self- administered OPAT at home showed savings of 93.73€ (37%) per OPAT day (only one study) and OPAT administered in an outpatient clinic or infusion centre showed mean savings 536.53€ (82%) (ranging from -47.59€ to -1861.64€ per day).

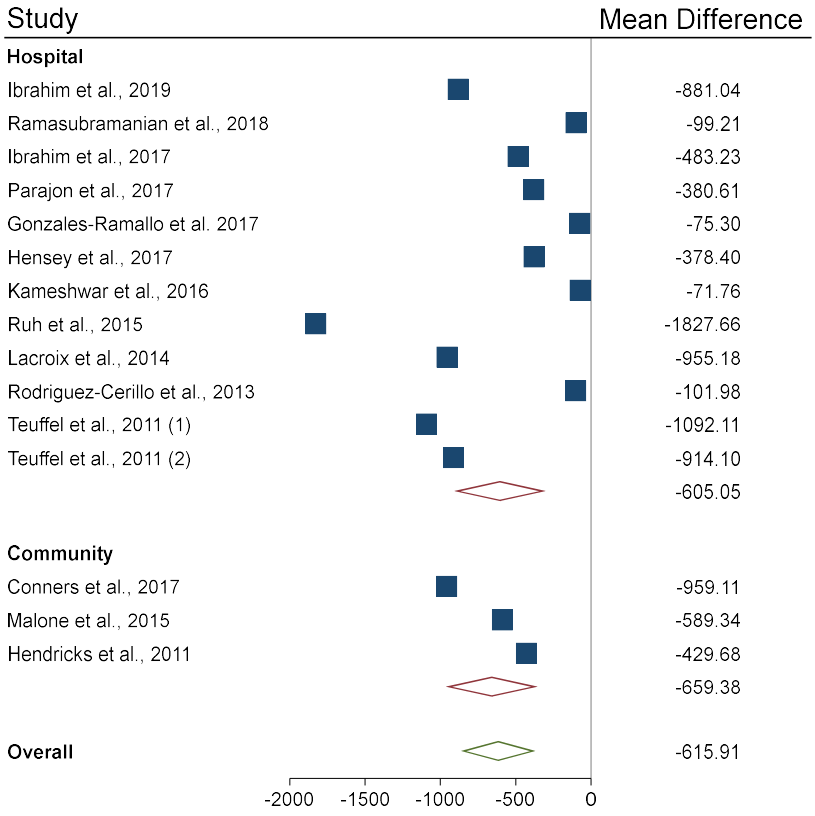
Analysing the OPAT setting with exclusion of support delivered by private health providers/hospitals showed more homogenise results (see Figure 11), OPAT at home (nurse-administered) showed mean savings of 615.91€ (56%) per OPAT day (ranging from -71.76€ to 1827.66€ per day), self-administered OPAT at home showed savings of 93.73€ (38%) per OPAT day (only one study), and OPAT administered in an outpatient clinic or infusion centre showed mean savings 94.82€ (50%) per day (ranging from -47.59€ to -175.47€ per day).

Figure 11: Cost difference per day (2019 - €) related to the different OPAT settings with exclusion of support delivered by private health providers/hospitals sorted by publication year



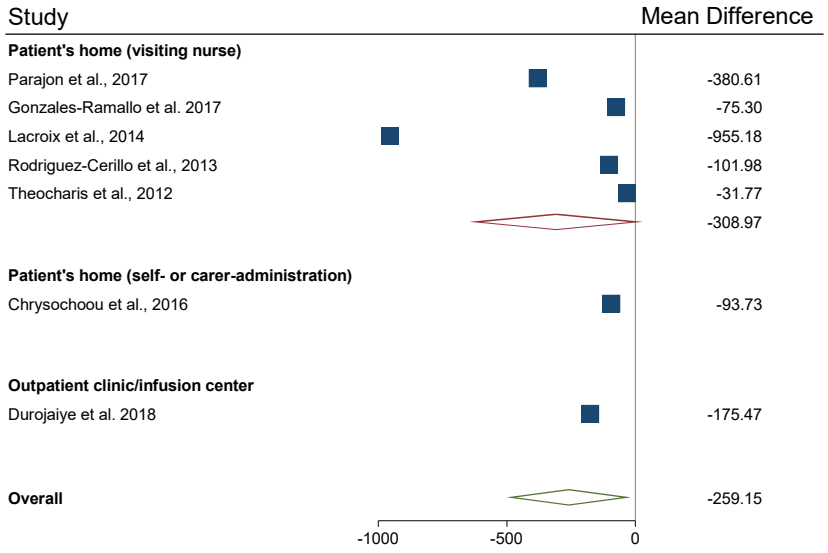
Analysis of OPAT in the patient's home (nurse-administered) showed similar results when delivered by either hospital or community support; the mean cost difference per day was -605.05€ (58%) for hospital support and -615.91€ (52%) for community support. See Figure 12.

Figure 12: Cost difference per day (2019 - €) per OPAT day with setting being the patient's home and either hospital or community support (studies sorted by publication year)



Analysing cost savings of the different OPAT delivery models for only Europe showed mean savings related to nurse administered OPAT in the patient's home of 308.97€ (42%) (ranging from -31.77€ to -955.18€ per day)(Figure 13), self-administered OPAT in the patient's home saved 93.73€ (38%) (only one study) and OPAT administered in an outpatient clinic or infusion centre saved 175.47€ (61%) per OPAT day (only one study).

Figure 13: Cost difference per day (2019 - €) per OPAT day for Europe related to the different OPAT settings (studies sorted by publication year)



Effectiveness results

Regarding mortality, our results did not suggest any differences between patients treated in the hospital or at home. Considering morbidity, we saw a tendency towards treatment failure being slightly reduced in the OPAT group, however non-significant. Resolution of infection was found to be significantly improved in the OPAT group compared to IPAT (31). In relation to lung function and clinical success no statistically significant differences were found between patients receiving OPAT compared to IPAT. The meta-analysis exploring readmissions revealed a non-significant tendency in favour of patients treated at home. Health related quality of life was reported significantly higher in one study (33) but two studies found no difference between groups (29, 32). Two studies investigated patient satisfaction and both found OPAT to be significantly associated with higher satisfaction compared to IPAT (38, 40) (see domain 4, EFF).

Four of the included original studies in the review performed cost-utility analyses based on health utility measurements (40, 82, 83, 93). In both studies by Teuffel et al. they elicited preferences by presenting hypothetical scenarios and was using a visual analogue scale to measure the patient's or parents' (in the study including children) preferences for the different treatment strategies. Effectiveness was expressed as quality adjusted febrile neutropaenia episodes, which was derived from the weighted average products of health state probabilities and health state utilities for each pathway in the model. The studies both concluded that outpatient management with intravenous antibiotics was the most cost-effective strategy as it was cost saving and more effective compared to intravenous treatment in the hospital.(82, 83).

In the study by Psaltidikis et al., health utilities were measured by applying the EQ-5D-3L questionnaire to 40 cases submitted to OPAT at the beginning and at the end of treatment. Utility was stratified to include four events; favourable outcome with no adverse effects; favourable outcome with adverse effect; treatment failure with hospitalisation or readmission; and death. QALYs were derived weighing the health state utility and probability for each model pathway. The study concluded that OPAT was the dominant strategy with lower costs and better quality of life (93).

Ibrahim et al. which studied children, used the Child Health Utility 9D questionnaire to obtain utility scores. The questionnaire was answered 24-48 hours after admission and 14 days after treatment completion. To obtain QALYs during treatment, initial utility scores were multiplied by the mean duration of the intervention. To obtain QALYs after completion, utility scores of the second measurement were multiplied by 14 days. The mean utility score as well as QALY during treatment was found to be higher in the home group compared to the hospital group. Scores after completion of treatment did not differ between groups. The study concluded that treatment at home was dominant and thus the most cost-effective strategy (40).

8.3.3 Discussion

Discussion of results

We included 28 studies in our systematic review, of which 21 contributed with data to the estimation of the average cost difference per day of OPAT compared to IPAT. Although there was insufficient evidence of how the cost analysis was conducted in most of the studies and only 12 studies supplying information of the included costing categories, patients allocated to OPAT had a significantly lower use of resources during their treatment process and hence lower cost for their treatment. Reduction in costs comparing OPAT to IPAT was found in all included original studies and appeared to be consistent within the different patient groups and for various OPAT delivery models. This finding is in accordance with results from other review articles, which we included in this report. All seven included review articles agreed that OPAT appears to be cost saving and therefore good value for money (22, 24, 25, 75-78).

According to the average cost savings reported in all 21 studies included in this systematic review, we found that OPAT could reduce treatment costs by 51% compared to IPAT corresponding to an average ratio of 3.3. This result is consistent with the comparable analysis performed in the review by Psaltidikis et al., who found general average economic savings per OPAT episode of 57% across the 35 included studies (25). The ratio of 3.3 of OPAT compared to IPAT was however slightly lower than the average ratio of 4.8 found in the review by Boese et al. (78), however the results indicate that relevant cost savings of OPAT could be expected when compared to IPAT.

Analysing the influence of study design on reported cost differences, we found that comparative studies reported lower cost savings when compared to studies with hypothetical IPAT comparators, finding cost reductions of 46% and 76% respectively. Similarly Psaltidikis et al. found that the comparative studies showed remarkably lower cost-savings, than studies estimating the hypothetical IPAT costs.

The financial structure of the health care system might influence the cost results. Therefore we performed the analyses of mean cost differences for the different continents. These analyses showed that studies from North America generally found larger average cost savings per day (67%) than studies from Europe (43%).

Analysing mean savings per day related to different age of the patient population, we found no systematic differences between children and adult populations. For the different conditions treated we also detected no systematic differences. Regarding the quality of the studies, it appeared that studies that were considered of low quality generally found smaller cost savings per OPAT day compared to studies in the better quality categories.

Looking into the different OPAT delivery models, we found that studies where OPAT was organised by an OPAT clinic or an OPAT Team showed larger cost savings per day (84%) than studies where OPAT was organised decentrally (average savings of 50%) or by a Hospital at Home/In the Home program (average savings of 45%). The same tendency were seen when considering only European studies. OPAT support

delivered by a private health provider/hospital showed the largest average cost saving per day (84%), whereas support delivered by either hospital or community showed similar cost savings per day, with average savings of 57% and 52% respectively.

The OPAT setting was analysed with exclusion of support delivered by private health providers/hospitals, assuming this would provide more comparable results to the Danish setting. These results showed that OPAT at home (nurse-administered) was found to be associated with average cost savings of 56% per OPAT day, self-administered OPAT at home showed savings of 38% per OPAT day (only one study), and OPAT administered in an outpatient clinic or infusion centre showed mean savings of 50% per day. When limiting the analyses of OPAT setting to include only European studies, we found following average cost savings per day; OPAT at home (nurse-administered) 42%, self-administered OPAT in the patient's home 38%, and OPAT administered in an outpatient clinic or infusion 61% (only one study).

Our results for OPAT at home (nurse-administered) and for OPAT administered in an outpatient clinic or infusion centre were very similar to the results found in the review by Psaltidikis et al., who found home health nursing to result in average savings of 57%, and infusion centres in savings of 57% (25). The proportion of included studies evaluating self or carer administration in our review (5%) differed significantly from the proportion in the review by Psaltidikis et al. (54%). This difference may be caused by our focus on intravenous therapies only, which was in contrast to Psaltidikis et al. who included multiple administration forms. Psaltidikis et al. found average savings of 62% for self or carer administration, whereas we found lower average savings of 38%. This deviance in results may reflect the difference in resource use related to different administration forms with intravenous therapies potentially introducing needs for more extensive support and training of the patient or carer than with other administration forms. This was exemplified by the included study in our review, which was evaluating children, whose parents were attending extensive training prior to OPAT at home (33). However, the results in our review had poor strength of evidence (only one study), and thus questionable generalisability.

One might speculate that OPAT will most likely imply a shift of costs from secondary to primary care, and may potentially introduce increased patient and family borne costs, however the two randomized controlled trials included in this review showed us the opposite. Hendricks et al. found patient/caregiver out of pocket costs to be significantly higher in the inpatient arm, however, they did not detect significant differences in costs related to informal care giving and lost work time between the two arms (29). Ibrahim et al. found that the total cost to family (absent from paid and unpaid work plus expenses during treatment) to be higher in the inpatient arm than in home arm (40). These results indicate that OPAT has the potential to reduce the family born costs associated with treatment.

Cost-effectiveness analysis is an integral part of health technology assessment and addresses the question of whether a new treatment or other health care program offers good value for money (95). Given that our review consistently showed that OPAT was less expensive and more effective than IPAT, the new strategy (OPAT) dominates the old one (IPAT). In this case, we did not need to estimate incremental cost-effectiveness ratio (ICER) or illustrate the cost-effectiveness acceptability curve (CEAC) because the efficiency-based decision rule is to adopt the OPAT strategy, however under careful clinical consideration of OPAT-suitable diagnoses and patient's resources.

In addition to the OPAT delivery models studied in our review of original studies, Psaltidikis et al. explored two different combined strategies, showing that combined strategies were associated with similar cost savings; combined strategy at home (i.e. self, caregiver and health nursing administration) showed average savings of 56 %, and combinations of infusion centres and home administration showed average savings of 53% (25).

Recently Minton et al. published an extensive report on behalf of the National Institute for Health Research (96), which studied the different OPAT service models in England: 1. hospital outpatient attendance, 2. specialist nurse visiting at home, 3. general nurse visiting at home, 4. self-administration or carer administration. Relating these UK models to our review and a Danish setting, general nurse might correspond to community nurses (e.g. district nurse), whereas specialist nurses have more expertise and may be comparable to hospital nurses.

In our review we did not detect any significant differences between hospital and community support. The economic assessment in Minton et al. used both Markov and simulation modelling methods, and data to populate the model came from systematic literature reviews and retrospective hospital data from seven OPAT centres (96). Thereby this report provided more detailed analyses, than possible in our review. The results of Minton et al. suggested that the specialist nurse visiting at home was the optimal service in the short term. In the long term, self-administration or carer administration appeared to be optimal, although the specialist nurse visiting at home model provided slightly higher benefits, but at a higher cost. The results also suggested that long-term infections may best be served by a combination of self-administration and specialist nurse visiting at home services (96).

Strengths and limitations

We included both available review articles and the original studies to conduct this review report using quality assessment checklists. The AMSTAR checklist is specifically designed for quality assessment of review articles and the Drummond checklist is used for critical assessment of economic evaluation. We are aware that most of the original studies were not conducted as an economic evaluation and therefore didn't receive high quality scores, simply because they were missing some important elements of an economic evaluation such as estimation of incremental cost and effectiveness.

Our systematic review has several limitations. Among 21 original studies that has been included in this systematic review, a small number of studies conducted a full economic analysis which followed a methodological guideline for economic-evaluation, therefore we ended up having only five studies which were classified as high quality according to Drummond's checklist (74) (scores 8, 9 and 10). The other moderate and low quality studies used simplified methods to calculate cost, especially calculation of the cost of IPAT was less complex than for OPAT. Additionally, the resources included in cost calculations varied, as did the unit costs for these components.

The individual studies were not directly comparable due to differences in patient population, inclusion criteria, follow-up period, OPAT strategy and organisation. This high heterogeneity in studies limited the ability to merge the findings from each individual study and perform a meta-analysis. In addition to considerable heterogeneity, nine studies estimated expenses related to hypothetical IPAT comparators rather than including real IPAT comparators in the study. The comparative studies based their analyses on collected original data, hence representing more scientific reliable results than hypothetical estimations, which were based on several assumptions and subject to major uncertainties. Furthermore, the estimations were not clear regarding each component of cost category during treatment process. Thus conclusions based on hypothetical estimations may lead to overestimation of expected cost savings.

Much of the studies in this area appeared to be based around service or effect evaluation and therefore, many of the studies provided only basic descriptive findings, with no estimates of variance (such as standard deviation or standard error). Therefore, our analyses were based on calculations of mean differences only, where all included studies were weighed equally without taking into account the variance, uncertainty and study size. In addition, due to missing information in the original studies, we were unable to assess the uncertainties

surrounding the results of mean differences in costs and calculate confidence intervals. Application of evidence will not be straight forward by having studies which did not follow the standard measures.

OPAT services have the potential to deliver significant cost savings and increased patient satisfaction for our health care system, but this information is key and must be reported in future studies if we are to identify best practice and support decision-making at a local level (96).

8.4 Micro-costing analysis in a Danish setting

The results of the economic literature may have limited transferability to a Danish setting, as financial structure and organisation of the health care system differs among countries. However, the consistent results showing that OPAT incurs cost savings imply that cost savings could be expected in the Danish setting as well, although the magnitude of the savings may be highly dependent on local organisation of the services.

With the aims of investigating the costs of the different care models for the delivery of OPAT in Denmark a complimentary micro-costing analysis was performed to better inform local decision making.

8.4.1 Methods

We performed the micro-costing analysis investigating different care models using a restricted societal costing perspective, thus including patient borne resource use and costs but excluding productivity costs.

Identification of relevant diagnostic cases for the description of the care models were performed through interviews and close cooperation with clinical informants under the criteria that selected diagnostic cases represented a high volume of patients as well as having several optional models of care (IPAT/OPAT). Moreover it was considered of great importance to selection that diagnostic cases represented different clinical specialties and different duration of treatment in the OPAT setting.

The selected diagnostic cases for the micro-costing analyses were following; spondylodiscitis (estimated OPAT treatment days: 21), febrile neutropenia (estimated OPAT treatment days: 5, pneumonia (estimated OPAT treatment days: 3), and acute pneumonia (no hospitalisation, estimated OPAT treatment days: 15).

Relevant care models based on selected diagnostic cases were described in close cooperation with clinical informants using an activity based approach to ensure that the models reflected actual clinical practice for each treatment strategy. Prescribed medication was an important factor influencing care model options within each diagnostic case, as stability data of the specific medication in different packaging (infusion bag, elastomeric pump etc.) determine possible delivery forms, and thus if or in which form the medication could be prepared as ready-to-use medication by the hospital pharmacy. Other factors highly influencing choice of model were e.g. patient's general condition, patient's wishes, and patient's possibilities of support by relatives meaning that not all described care models were suitable for all patients, but must be carefully considered based on clinical expertise and shared decision making.

The various described care models were in total:

- Inpatient stay
- Outpatient treatment (hospital)
    - Model 1 (daily infusion in the outpatient clinic)

  - Model 2 (electronic pump + daily visit in the outpatient clinic), where the patient was visiting the hospital for daily treatment start-up using an electronic pump.
  - Model 3 (elastomeric pump + daily visit in the outpatient clinic), where the patient was visiting the hospital for daily treatment start-up using an elastomeric pump.

- Outpatient treatment (infusion-/health centre),
  - Model 1 (daily infusions in the infusion/health centre)
  - Model 2 (electronic pump + daily visit in the infusion/health centre), where the patient was visiting the infusion/health centre for daily treatment start-up using an electronic pump.
  - Model 3 (elastomeric pump + daily visit in the infusion/health centre), where the patient was visiting the infusion/health centre for daily treatment start-up using an elastomeric pump.

- Home-IV (community nurse),
  - Model 1 (community nurse visit for each infusion)
  - Model 2 (electronic pump + community nurse), where a community nurse visited the patient's home to start treatment using an electronic pump,
  - Model 3 (elastomeric pump + community nurse), where a community nurse visited the patient's home to start treatment using an elastomeric pump,

- Home-IV (self-administration)
  - Model 1 (electronic pump + tele-monitoring), the patient was administering his/her own treatment in the home using an electronic pump and daily measurements were performed and reported by the patient using tele-monitoring,
  - Model 2 (elastomeric pump + tele-monitoring), the patient was administering his/her own treatment in the home using an elastomeric pump and daily measurements were performed and reported by the patient using tele-monitoring,
  - Model 3 (duplex/divibax, no pump + tele-monitoring), the patient was administering his/her own treatment in the home without use of pumps. Daily measurements were performed and reported by the patient using tele-monitoring.

Resource use and costs were identified by carefully describing processes and needed equipment/utensils within each activity in the different models of care. The analyses applied a marginal costing approach, hence focusing on processes and procedures that differed between models and excluding activities and costs common to all compared models within each selected diagnostic case.

Resource use within each clinical activity of the care models was estimated through interviews with skilled clinical informants based on their practical experience. Activities and associated resource use is presented in Appendix 10. Number of daily administrations depended on the diagnosis being treated and the specific medication. For medications requiring multiple daily administrations, a number of three daily administrations was included in the care models, based on most common clinical practice. For inpatients we assumed one daily

clinical evaluation and for patients treated in an OPAT setting we assumed one clinical evaluation in the hospital per seven treatment days. The estimated time required for a clinical evaluation was 15 min nursing and 15 min physician time.

Nursing time related to the infusion with regular medication was estimated to be 30 min in the hospital (in- or outpatient) or infusion-/health centre, where more patients might be treated simultaneously. Required nursing time in the patients' home using regular medication nurse was highly dependent on the administration time. The mean duration of the infusion was estimated by clinicians to be 30 min, thus the mean nursing time for a community nurse in the patient's home was estimated to be 45 min except for the first visit, which was one hour. For patients, where the treatment was administered by either electronic or elastomeric pump, the nursing tasks were less time consuming, as she/he was to only change the pump/infusion bag and start the infusion, thus the required nursing time was estimated to be 25 min (45 min for the first visit), allowing for time to run blood test and regular monitoring.

For patient's treated at home we assumed one weekly pick-up of medication in the hospital estimated to require 15 min nursing time. In the OPAT care models we assumed 1 change of MID-line/PICC-line when number of treatment days exceeded seven. Change of MID-line/PICC-line was estimated to require 30 min nursing and 30 min physician time.

Administration included paperwork, documentation and communication between hospital nurse and community nurse and/or the patient as well as including daily check of clinical values, when tele-monitored by the patient. It was assigned once per treatment day in home-IV scenarios and had an estimated nursing time of ten min.

Training session included supply of information and patient training (pump/tele-monitoring) and was assigned whenever the care model included either electronic or elastomeric pump. The estimated nursing time performing patient training was three hours allowing for patients to practice and demonstrate self-administration in the hospital.

In the self-administration models of care we assumed one telephone or email consultation every twice per week of treatment.

Average travel distance from hospital to the patients home were assumed to be 14 km as recommended by the Danish Medicines Council (97). An argument for introducing OPAT is to offer treatment closer to or in the patients home, thus the travel distance from the infusion-/health centre to the patient's home was assumed to be half the travel distance to the hospital (7 km). Travel costs for patients t/r to hospital was estimated to be 13 € as recommended by the Danish Medicines Council (97), which was assumed to be halved t/r to infusion-/health centre. Waiting time in the outpatient clinic or infusion-/health centre was assumed to be 13 min, according to the mean waiting time in medical outpatient facilities found in a Danish study (98).

Number of treatment days in the OPAT setting for each diagnosis was based on estimated means stated by clinical experts, however for pneumonia assumptions were made based on clinical data from Akutteam Odense (99), and for full OPAT treatment of acute pneumonia the assumption of treatment duration was based on trim point for the diagnosis using the Danish DRG-system (100). Number of daily infusions were determined by the specific prescribed medication and delivery form and information was obtained from hospital pharmacies and clinical experts.

Resource use was valued using several different sources (Appendix 11). Danish kroner were converted into Euros using an exchange rate of 0.13.

Although hospitals in Denmark are no longer financed based on DRG-activities but financially governed through value-based principles and overall budgets, The Government and the Danish Regions agree that activities calculated as DRG production value persists as a central and valid part of monitoring health care activities and for calculation of co-financing from the municipalities. Therefore relevant DRG-tariffs were included as part of the micro-costing analyses. Under the assumption that the OPAT treatment, for inpatients who were receiving the last part of their treatment in an OPAT setting, exceeded the length of treatment already included in the DRG-tariff for their admission, we applied the bed day tariff (100) as the IPAT alternative. As the bed day tariff only includes costs of stay we added the estimated costs of IV treatment (nurse time), daily clinical evaluation (nurse and physician time) and medication costs. For acute outpatients who were directly transferred to treatment in an OPAT setting, hospitalisation was avoided and thus the IPAT alternative was considered the DRG-tariff for the admission, which would have been the cost had the patient not had the OPAT option.

Resource use was valued using average national hourly costs for nurses, physicians and patients as recommended by the Danish Medicines Council (97). The recommended hourly costs were calculated using gross hourly wage multiplied by a factor of 2 to include costs for overhead, time for non-patient-related tasks, breaks and absences other than holidays. However, in municipalities non-patient-related tasks such as travel time constitute a larger amount and patient-related time a smaller amount of the total working hours than in hospitals. To account for this difference in patient-time percentage and to incooperate travel time costs in the hourly salary the recommended national hourly costs for community nurses treating patients in their home were multiplied with factor 1.25. For community nurses in infusion-/health centres we used the plain recommended hourly cost. Travel costs for community nurses were assumed to be covered by the overhead costs already assigned the hourly costs.

For patient travel cost we used the national reimbursement rate, assuming total annual km driven was below 20,000. Medication costs were obtained from the hospital pharmacies in the Central Denmark Region and Funen. Costs of ready-to-use medication prepared in the hospital pharmacies (infusion bags and elastomeric pumps) included medicine, utensils and production costs. The daily medication cost was calculated as the cost per dose added the cost of natriumclorid and infusion set, where relevant, and multiplied by the number of daily doses.

Daily cost of the electronic pump (CADD Solis) were calculated as follows: Assumed cost of the electronic pump and carriers bag was 2600 € and 78 € respectively, which was calculated as an equivalent annual cost, using an estimated life time of five years and an interest rate of 0%. Annual costs of service, cleaning and nurse education were added the equivalent annual cost. The annual costs were calculated as daily operating cost assuming 150 days of use per year. Daily cost of batteries and infusion set were added to the daily operating cost to get the total daily cost of the electronic pump.

Tele-monitoring costs were divided into start-up and running costs. Tele-monitoring start-up costs included cleaning, disposable leaflet, and CRP-kit for each patient. Tele-monitoring running costs were calculated as follows: Assumed cost of tablet and monitoring devices (tele-kit) was 1300 €, which was calculated as an equivalent annual cost, using an estimated life time of five years and an interest rate of 0%. Annual licence, service costs and IT-running costs were estimated based on data from the TeleCare Nord study (101) assuming a volume of 10,000 tele-kits. Total running costs were calculated as a daily cost assuming 150 days of use per year.

Analyses

Relevant care models for each selected diagnostic case were assigned the specific clinical activities and the total cost of the treatment episode was calculated. To compare costs across diagnostic cases we calculated the cost per treatment day as total cost of the episode divided by the specific number of treatment days. Cost differences per treatment episode for the care models in each diagnostic case were calculated with inpatient stay as the comparator.

Sensitivity analyses

Sensitivity analyses should ideally test the robustness of the results when varying uncertain parameters in the analyses. The models of care were all carefully described in cooperation with clinical experts but are based on assumptions using average parameter estimation, knowing that there is no such thing as an average patient or average course of treatment. Thus in principle all parameters were subject to uncertainties and could be varied through multiple sensitivity analyses. However, as one of the the main cost drivers in the OPAT models were the salary of community nurses, and because the patient-time percentage varies largely across regions being highly dependent on travel distances in municipalities, we decided to perform one way sensitivity analyses varying this parameter only. The analyses applied an interval of hourly staff costs using the hourly staff cost recommended by the Danish Medicines Council as lowest and the recommended hourly staff cost multiplied by factor 1.5 as highest value.

8.4.2 Results

Results from micro-costing analyses of all relevant care models within each diagnostic cases can be found in Appendix 12. As treatment of spondylodiscitis clinically consists of the use of one of two medications (ceftriaxone or cefuroxime), which differ in number of infusions per day and possible delivery forms, two independent analyses were performed for this diagnostic case.

Table 10 shows the total treatment cost per episode and the cost per treatment day for all relevant care models in each included diagnostic case. 'Not applicable' marks models where either the possible delivery form of the specific medication did not support the specific treatment option or cases where number of infusions makes the treatment option clinically irrelevant.

As an example of 'not applicable: To use the electronic pump antibiotics must either be prepared in an infusion bag in the hospital or from the hospital pharmacy as ready-to-use infusion bag. Stability date of the specific medication determines if it is relevant for the pharmacy to prepare it as ready-to-use medication. Due to aseptic preparation ready-to-use medication prepared in the pharmacy often present an extended durability compared to medication prepared in the hospital that in general has a durability of 24 hours. If medication can be delivered from the hospital pharmacy as ready-to-use, it allows for patients to bring medication for several days for either treatment at home or in an infusion/health center. In cases like cefuroxime for spondylodiscits it is possible for the hospital to prepare three infusions of the medication in an infusion bag with durability of 24 hours, however, the specific medication is at present not delivered ready-to-use from the involved hospital pharmacies. This means that care models using an electronic pump for this medication is only applicable when patients visit the hospital outpatient clinic every day during their treatment.

Additionally, all the analysed care models may not be optional in all Danish regions, as the models are highly dependent on the assortment of ready-to-use medication in the regional hospital pharmacy.

Table 11 shows the cost differences per treatment episode with inpatient stay as comparator. The results showed that OPAT care models were the less costly than hospitalisation. The relative cost reduction varies

largely between care models, however models with less use of health care services generally present the most substantial cost reductions. Sensitivity analyses of cost differences varying the factor of travel time for community nurses can be found in Appendix 13-14.

Table 10: Total cost per episode and per treatment day related to the model of care, presented by diagnostic case (2020-€)

	Treatment for 21 days after hospitalisation Case: Spondylodiscitis *Medication: Ceftriaxone*		Treatment for 21 days after hospitalisation Case: Spondylodiscitis *Medication: Cefuroxime*		Treatment for 5 days after hospitalisation Case: Febrile Neutropenia *Medication: Piperacillin/Tazobactam*		Treatment for 3 days after hospitalisation Case: Pneumonia *Medication: Piperacillin/Tazobactam*		Treatment for 15 days, hospitalisation avoided Case: Acute pneumonia *Medication: Piperacillin/Tazobactam*	
Care model	*Cost per episode*	*Cost per day*	*Cost per episode*	*Cost per day*	*Cost per episode*	*Cost per day*	*Cost per episode*	*Cost per day*	*Cost per episode*	*Cost per day*
Inpatient stay	7913	377	9535	454	2308	462	2113	704	4817	321
Outpatient treatment (hospital)										
Model 1 (daily infusions in the outpatient clinic)	1782	85	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Model 2 (electronic pump + daily visit in the outpatient clinic)	2393	114	2509	119	728	146	523	174	1994	133
Model 3 (elastomeric pump + daily visit in the outpatient clinic)	3538	168	Not applicable	Not applicable	1039	208	671	224	2734	182
Outpatient treatment (infusion/health centre)										
Model 1 (daily infusions in the infusion/health centre)	2125	101	4530	216	1287	257	606	202	3333	222
Model 2 (electronic pump + daily visit in the infusion/health centre)	Not applicable	Not applicable	Not applicable	Not applicable	1383	277	664	221	2763	184
Model 2 (elastomeric pump + daily visit in the infusion/health centre)	3886	185	Not applicable	Not applicable	1514	303	743	248	3157	210
Home-IV (community nurse)										
Model 1 (community nurse visit for each infusion)	2530	120	5456	260	1247	249	757	252	4492	299
Model 2 (electronic pump + community nurse)	Not applicable	Not applicable	Not applicable	Not applicable	861	172	588	196	2529	169
Model 3 (elastomeric pump + community nurse)	3613	172	Not applicable	Not applicable	992	198	667	222	2924	195
Home-IV (self-administration)										
Model 1 (electronic pump + tele-monitoring)	Not applicable	Not applicable	Not applicable	Not applicable	629	126	520	173	1901	127
Model 2 (elastomeric pump + tele-monitoring)	2706	129	Not applicable	Not applicable	822	164	599	200	2295	153
Model 3 (Duplex/Divibax + tele-monitoring)	1294	62	1707	81	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Table 11: Cost differences per treatment episode (2020-€ and %) using inpatient stay as comparator

	Treatment for 21 days after hospitalisation Case: Spondylodiscitis *Medication: Ceftriaxone*		Treatment for 21 days after hospitalisation Case: Spondylodiscitis *Medication: Cefuroxime*		Treatment for 5 days after hospitalisation Case: Febrile neutropenia *Medication: Piperacillin/Tazobactam*		Treatment for 3 days after hospitalisation Case: Pneumonia *Medication: Piperacillin/Tazobactam*		Treatment for 15 days, hospitalisation avoided Case: Acute pneumonia *Medication: Piperacillin/Tazobactam*	
	COMPARATOR: INPATIENT STAY									
Care model	*Δ Cost per episode*	*%*	*Δ Cost per episode*	*%*	*Δ Cost per episode*	*%*	*Δ Cost per episode*	*%*	*Δ Cost per episode*	*%*
Inpatient stay	7913	-	9535		2308	-	2113	-	4817	-
Outpatient treatment (hospital)										
Model 1 (daily infusions in the outpatient clinic)	-6131	-77%	Not applicable	-	Not applicable	-	Not applicable	-	Not applicable	-
Model 2 (electronic pump + daily visit in the outpatient clinic)	-5520	-70%	-7027	-74%	-1581	-68%	-1590	-75%	-2823	-59%
Model 3 (elastomeric pump + daily visit in the outpatient clinic)	-4375	-55%	Not applicable	-	-1270	-55%	-1442	-68%	-2083	-43%
Outpatient treatment (infusion/health centre)										
Model 1 (daily infusions in the infusion/health centre)	-5788	-73%	-5006	-52%	-1021	-44%	-1508	-71%	-1484	-31%
Model 2 (electronic pump + daily visit in the infusion/health centre)	Not applicable	-	Not applicable	-	-926	-40%	-1449	-69%	-2054	-43%
Model 2 (elastomeric pump + daily visit in the infusion/health centre)	-4026	-51%	Not applicable	-	-794	-34%	-1370	-65%	-1659	-34%
Home-IV (community nurse)										
Model 1 (community nurse visit for each infusion)	-5383	-68%	-4080	-43%	-1062	-46%	-1356	-64%	-325	-7%
Model 2 (electronic pump + community nurse)	Not applicable	-	Not applicable	-	-1447	-63%	-1525	-72%	-2287	-47%
Model 3 (elastomeric pump + community nurse)	-4300	-54%	Not applicable	-	-1316	-57%	-1446	-68%	-1893	-39%
Home-IV (self-administration)										
Model 1 (electronic pump + tele-monitoring)	Not applicable	-	Not applicable	-	-1679	-73%	-1593	-75%	-2916	-61%
Model 2 (elastomeric pump + tele-monitoring)	-5207	-66%	Not applicable	-	-1487	-64%	-1515	-72%	-2521	-52%
Model 3 (Duplex/Divibax + tele-monitoring)	-6619	-84%	-7828	-82%	Not applicable	-	Not applicable	-	Not applicable	-

8.4.3 Discussion

Discussion of results

Findings from the micro-costing analyses in a Danish setting using different diagnostic cases supported the overall conclusion from the literature review; that OPAT-delivery was associated with reductions in treatment costs. Not surprisingly models of care with less need for health care services and support by health care staff showed the largest cost reductions compared to hospitalisation. Sensitivity analyses did not alter these overall results. A recent Danish report evaluated the economic consequences of Akutteam Odense, a community based emergency team. Delivery of OPAT treatments was only one of several activities performed by the team, and costs of the different team activities were not independently analysed, thus it was not possible to assess the costs or potential cost savings resulting from OPAT, but the overall conclusion was that the activities of Akutteam Odense resulted in significant savings whereof 54% were due to prevented hospitalisations for IV treatment (102).

It must be noted that the cost-differences presented in the micro-costing are analytical calculations and should not be used in comparing the different models of care, as the different models are unlikely to be suitable for the same patients. This means that different OPAT-models target different types of patients e.g. self-administration models are suitable for resourceful patients, whereas the model with community nurse administering the treatment in the patients home is suitable for vulnerable patients presenting less resources. Thus the different OPAT-models address a range of different patient needs from the possibility to continue the everyday life at home during treatment to the possibility of offering protected and individual care in a quiet and familiar environment.

Strengths and limitations

The micro-costing analyses using diagnostic cases were developed in close cooperation with clinical experts. Models of care were subsequently validated consulting the same clinical experts to ensure that activities and estimated associated resource use followed their clinical input and reflected actual clinical practice. Resource use other than clinical activities were, wherever possible, estimated using available study results or national recommendations. Valuation of resource use was based on several different sources; recommendations, guidance reports, information from hospital pharmacies, and calculations using study data or information from experienced experts.

However, the performed analyses had several limitations. The basic premise of using average parameter estimations meant that reality was simplified for the purpose of analysing. This results in an otherwise complex reality appearing simple without reflecting potentially important nuances and differences. Although the analyses carefully attempted to mimic actual clinical practice exemplified by the selected diagnostic cases, activities and resource use will most likely differ across different hospital settings.

The analysed models of care were structured into cathegories following the organisational structure of OPAT support in a Danish setting. It might be argued that e.g. use of electronic or elastomeric pumps under the outpatient hospital cathegory is not actually outpatient treatment, but outpatient assisted self-administration. However, the described models were cathegorised as chosen to maintain transparency in the analytical process, knowing that the complexity of the OPAT-models might be simplified and very well cathegorised differently. Moreover, the micro-costing analyses were based on current practice and as OPAT opportunities are rapidly evolving, it is very likely that the analyses and results will appear inaccurate at the same pace.

The analysed OPAT models of care included three daily antibiotic administrations, as this number of administrations, according to clinical experts, is most common in daily practice. However, some patients may receive up to four daily administrations and especially in the care model, where patients receive visits from the

community nurse for each administration, the additional administration will influence the costs making the specific care model more costly. Conversely, fewer administrations than three will result in care models being less costly. These variations in number of i.v.administrations were not reflected in the micro-costing analyses.

Optional OPAT-models and ready-to-use assortment in the present analyses was based on information two hospital pharmacies. Thus the analyses illustrated the possible OPAT-models in the supply area of these pharmacies. Therefore, regional variations may very well exist, which is not reflected in the analysis.

For community nurses, treating patients at home, the patient-related time generally constitutes a smaller percentage of the total working hours than for hospital nurses. This is caused by the considerable amount of time used for transport, which is a prerequisite when visiting the patients. The magnitude of travel time will, however, vary largely across municipalities depending on their geographical size as well as the population density. In Danish municipalities prices per delivered patient-related hour are calculated within each municipality using a standardised model devolped and recommended by Local Government Denmark (KL). The model calculations are based on long term costs including travel time, overhead and patient-time percentage. Although being aware of these regional/municipality differences in calculations of staff cost, the micro-costing analyses were based on the hourly nursing cost recommended by the Danish Medicines Council for both regional and community nurses. To account for the differences in patient-time percentage following the travel time for community nurses visiting patients' home, this specific hourly cost was multiplied by factor 1.25, and sensitivity analyses were performed to address variations.

The organisational analyses revealed differences in expressed needs for educational training of nurses in the community setting. Educational training of community nurses was not included in the cost analyses but could be regarded an investment cost. Establishment and upscaling of community services may be associated with significant costs, however not reflected in the micro-costing analyses, as these costs will vary largely across communities and inclusion of these costs could lead to over-estimation of the running cost of OPAT. Costs of continously training of community nurses was assumed to be comparable to continuously traning of hospital nurses, and was not included in the marginal cost analyses.

Costs of the electronic pump and tele-monitoring devices were conservatively estimated without considering possible volume discounts. Investment costs were amortised to an annual cost and an estimated daily operating cost was calculated assuming 150 annual days of use. The annual days of use were again a conservative estimate, as the expected days of use will most likely be higher when OPAT is implemented to a higher extend. The conservative estimates may lead to an overestimation of the costs of the electronic pump and tele-monitoring, however the impact on total scenario costs is considered to be of limited importance.

The micro-costing analyses were performed under the assumption that patients follow the chosen model of care until end of treatment. Real situations will often arise, where patients' needs and preferences change during the course of treatment, flexibility is important and shift of treatment option is a way of meeting these changes. Although relevant, the presented analyses did not take combinations of the different care models into account.

The costs analyses were performed from a restricted societal costing perspective excluding productivity costs. However, in some of the OPAT care models, where self-adminitration is optional, patients might be able to resume work earlier than when hospitalised, thus self-administration models may have the potential to reduce societal costs in some cases. The micro-costing analyses did not reflect this potential societal value as well as the analyses did not reflect the potential added value of patient time spend in a home-setting compared patient time spend in the hospital.

List of informants who provided input for the economic analyses is presented in Appendix 15. We thank you for your cooperation and valuable conversations.

8.5 Important considerations regarding implementation of OPAT

The following section presents considerations emerged through the performed interviews with different informants, when gathering information for the micro-costing analyses. The considerations should be regarded as input for decision-makers when discussing important issues relevant to the implementation of OPAT in a Danish setting.

What level of service should be offered in the healthcare system?

As mentioned in the micro-costing analyses, the OPAT-models are clearly not a "one-fits-all" solution and choice of care model should be clinically based on careful visitation taking into account the specific patient's' needs and resources. Hence, when aiming at enhancing patient centred care, a larger selection of care models will increase the probability of being able to meet the patients' individual preferences and clinical needs, making economic arguments seem secondary. If, instead of focusing on individual patient needs, a macro perspective is applied, the important issue to discuss is, what level of service should be offered in the healthcare system. Political agreement and preparation of national guidelines may build upon economic considerations, and general patient criteria for being offered the different care models may guide clinical staff into a systematic harmonised practice as well as serving as means of controlling costs.

Choice of pump is of clinical importance

When it is appropriate to use the electronic pump and when it is appropriate to use an elastomeric pump will vary. From a health sector perspective one does not exclude the other.

The use of CADD-solis VIP infusion pump, is associated with a significant investment when purchasing the electronic pump (2600 €). Although the micro-costing analysis showed that the operating cost of the electronic pump was in line with the cost of the elastomeric pump, the cost of purchasing the electronic pump may be crucial to a local department in relation to implementing this solution.

The CADD infusion pump weighs 500 grams, which restricts the use in relation to carrying around both the pump and the infusion bag e.g. in treatment of small children or debilitated elderly patients. The elastomeric pump is easier to carry around and with the elastomeric pump, it is also easier to change the dose between treatments.

Both pumps require resources for training and introduction of staff, both initially for implementation but also continuously in relation to new staff. Additionally, the patient must also be instructed in use of the pumps and the electronic pump can be more technically challenging for the patient than the elastomeric pump e.g. in case of alarm or battery replacement. However, the design of the electronic infusion pump has been developed with an intuitive patient-focused user interface, where the treatment-related information appears in an easy-to-understand format.

The CADD-solis VIP pump has 5 different administration modes (eg continuous or intermittent) and can therefore be used in several different courses of treatment and diagnostic groups compared to the elastomeric pump, which can only infuse continuously.

Another important aspect related to the choice of pumps is the their flow rate accuracy, as deviations from nominal flow rate may be clinically significant for the person being treated. Elastomeric infusion pumps are required by regulatory testing standards to maintain an average flow rate that is within ±15% of the nominal flow rate for the pump when tested under the operating conditions. However, test conditions in the laboratory setting may differ from conditions in the home environment, and variation in environmental factors may lead

to variation in average flow rates of up to ±40% with elastomeric infusion pumps (103). A recent study investigated the impact of changes in infusion pump height and/or back pressure on flow rate and the volume of infusion solution delivered comparing four different elastomeric and one electronic pump. The study found that flow rate and volume delivered by the elastomeric pumps varied considerably under different conditions and between the tested pumps, whereas conditions had little effect on the electronic pump (104).

When choosing pump options it is therefore important for clinicians to carefully consider factors such as the characteristics of the individual patient, environmental factors (e.g. the home environment), half-life, therapeutic window and safety profile of the medication to be infused, as well as the goals of treatment when determining the use of pump.

These issues underlines the previous conclusion, that different OPAT-models are suitable for different patients and should be considered as supplementing alternatives instead of comparators.

Harmonisation of regional differences may minimise costs and ensure equality

In a Danish setting, regional variations were detected related to different pharmacies having different ready-to-use assortments. Possible delivery forms are, as before mentioned, dependent on the stability and durability of the medication in different packaging and in addition also dependent on the production facilities in the hospital pharmacies. Ready-to-use solutions may be delivered from the pharmaceutical companies but in a Danish setting the ready-to-use medication is most likely prepared by the hospital pharmacies. Our investigation detected differences in possible delivery forms of the same medication across regions as well as differences in available pump-solutions (elastomeric/electronic). This reflects the fact that local decisions made in the different regions or regional hospital pharmacies result in geographic variations in optional OPAT care models. As a result, patients experience that what is possible in one hospital might not be possible in another, which may give rise to frustrations e.g. in courses of treatment, where the patient is transferred from one hospital to another. Nationally aligned OPAT-possibilities, agreed assortment of medication, and coordinated preparation of ready-to-use medication in the hospital pharmacies could limit variability as well as potentially lower medication costs, due to volume consideration and efficient organisation.

8.6 Conclusion

We included 28 studies in our systematic review, of which 21 of them contributed data to the estimation of the average cost difference per day of OPAT compared to IPAT. Reduction in costs comparing OPAT to IPAT was found in all included original studies and appeared to be consistent within the different patient groups and for various OPAT delivery models. This finding is in accordance with results from other review articles, which we included in this report. All seven included review articles agreed that OPAT appears to be cost saving and therefore good value for money.

Considering the effectiveness OPAT was generally found to be as effective or more effective than IPAT in the included outcomes. Thus, as OPAT was found to be less expensive and more effective than IPAT, the new strategy (OPAT) dominates the old one (IPAT). In this case, we did not need to estimate incremental cost-effectiveness ratio (ICER) or illustrate the cost-effectiveness acceptability curve (CEAC) because the efficiency-based decision rule is to adopt the OPAT strategy, however under careful clinical consideration of OPAT-suitable diagnoses and patient's resources.

The results of the economic literature may have limited transferability to the Danish setting, as financial structure and organisation of the health care system differ among countries. However, the consistent results showing that OPAT incurs cost savings imply that cost savings might be expected in the Danish setting as well, although the magnitude of the savings may be highly dependent on local organisation and delivery of the services.

With the aims of investigating the cost differences in a Danish setting to better inform local decision making, we performed a complimentary micro-costing analysis informed through interviews with clinical experts. Findings from the micro-costing analysis using different diagnostic cases supported the overall conclusion from the literature review; that OPAT care models were associated with a reduction in treatment costs. Not surprisingly care models with less need for health care services and support by health care staff showed the largest cost reductions compared to hospitalisation.

It must be noted that the cost-differences presented in the micro-costing are analytical calculations and should not be used in comparing the different models of care, as the different models are unlikely to be suitable for the same patients. Thus the different OPAT-models address a range of different patient needs from the possibility to continue the everyday life at home during treatment to the possibility of offering protected and individual care in a quiet and familiar environment. Hence the investigation of OPAT-models made it clear that there is no "one-fits-all" solution and choice of care model should be based on careful visitation taking into account the specific patients' needs and resources.

Additionally the investigation identified important issues that may influence OPAT implementation and related costs, and should be carefully considered by decision makers. These issues were; What level of service should be offered in the healthcare system?, Choice of pump is of clinical importance, Harmonisation of regional differences may minimise costs and ensure equality, and Regional / municipal cooperation.

9 MAIN FINDINGS

In this Health Technology Assessment (HTA), Outpatient Parenteral Antibiotic Therapy (OPAT) are examined and compared to conventional Antibiotic Treatment in the hospital, with the purpose of establishing a basis for decision-making regarding how OPAT should be integrated as an alternative to in-hospital treatment. In this report OPAT refers to outpatient management of an infection via the administration of an intravenous (IV) antibiotic medicine *without* an overnight hospital stay. IPAT refers to inpatient management of an infection via the administration of an IV antibiotic *with* one or more overnight hospital stay(s). The HTA has been produced at the request of the Health Directors in the five Danish Regions, and it was deemed highly relevant to discover the preconditions for and consequences of introducing OPAT, using a HTA approach. Within the given framework of this report, we will focus into topics of highest relevance to the five regions, knowing there will be areas, that cannot be fully covered.The scope of the report can be found in Domain 1, and general methods in Domain 2.

Description and technical characteristics of technology and patient description (TEC)

OPAT refers to outpatient management of an infection via the administration of an intravenous (IV) antibiotic medicine without an overnight hospital stay. The selection of patients with infection, who are suitable for OPAT is essential. Patients with severe acute infections and those, who require close monitoring or adjunctive therapies are not good candidates for OPAT and should be managed as inpatients. Frequent infections treated with OPAT regimes include patients with lung infection, urinary tract infection, stable endocarditis, neuroborreliosis, osteoarticular infections, infections at surgical sites, infections with multidrug resistant bacteria, and skin and soft-tissue infections. Patient selection should also consider e.g. severity, patient mobility, stability of comorbidity and family and self-care capacities.In OPAT as well as IPAT intravenous (IV) catheters are an essential part in the process of IV antibiotic treatment. Suitable vascular access devices (VAD) depend on e.g. patient wish, the duration of OPAT, and patient-related conditions such as vascular status, risk of bloodstream infections and thrombosis. VAD include devices such as Peripheral venous catheter (PVC), Central venous catheter (CVC), Peripherally inserted central catheter (PICC) and Midline.Steril and safe handling of the antibiotics to protect both patient, staff and environment is paramount. Examples off ready-to use drug systems include Duplex (a dual chamber IV container that stores the drug and diluent in separate compartments until administration), Elastomeric Pumps, Prefilled bags and syringes and Divibax (a medicine mixing system).

Clinical effectiveness (EFF) and Safety (SAF)

In 11 peer-reviewed RCT and observational studies OPAT were compared to IPAT in different settings, patient groups and in relation to different out-come. This remains a challenge in relation to transferability of the results. Overall, the quality of the evidence in relation to the results in this Domain is very low, partly based on the design of the studies (observational studies) and partly on an assessment of the quality and impressision of the estimates. In relation to 'clinical success', 'readmission', 'resolution of infection' and 'treatment failure' minor to moderate insignificant differences primarily in favour of OPAT were found. In relation to 'Quality of life' and 'satisfaction' minor to moderate significant differences were found in favour of OPAT. Similar results were found in other systematic reviews. Although results point in the same direction, that OPAT performs equivalent or better than IPAT, these results need confirmation from future prospective well-designed clinical studies.

On the basis of included studies OPAT is found to be a safe model of health-care delivery in treatment of patients with various infections. In general a low incidence rate was found in relation to safety outcomes such as morbidity, complications, adverse serious advents and treatment failure with no overall difference between the groups. However, a few of the studies indicated a lower frequency of adverse serious events, treatment failures and complications in the OPAT group compared with the IPAT group.

Patient & Social (SOC)

Conclusions were based on nine qualitative studies and one survey study. Overall studies were of acceptable quality. A main point from the patient perspective is the importance of selecting the right patients for OPAT. Important factors to consider before initiating OPAT are; patients' mobility in general, comorbidity, family circumstances, social resources, care giver resources', the condition of the home etc. One of the most appreciated aspects of OPAT is the possibility to enjoy the comforts of the home. Being at home increases the feeling of freedom and normality. For children being treated with OPAT, being at home is a chance for the whole family to be together. However, moving treatment from the hospital to the home can sometimes create worry and fear of possible complications. A reassuring factor is knowing who to contact in case of questions or needed assistance. Generally, the ability to ask questions before and during treatment empowers patients to be actively involved in the treatment. Clear communication about the course of treatment, practicalities, possible side effects and what to expect from OPAT, altogether create a feeling of security. To be an OPAT patient, generally takes up more time than expected as everyday life has to be adjusted around the treatment. Nevertheless, most patients prefer treatment at home compared to inpatient treatment. Following this conclusion, it is important to remember that most patients in the included studies only have experiences with one of the treatment pathways. Therefore, they are not able to compare the different treatment pathways, but express a general desire to be treated at home.

Organisational (ORG)

The organisational domain is based on regional and national documents for the implementation and use of OPAT, studies of mainly descriptive character, and on qualitative interviews with leaders, administrative employees and health professionals involved in the delivery of OPAT.

The analysis shows that the organisation of OPAT varies in Denmark but also internationally. In a Danish context, there are three general delivery models of OPAT, defining the type of administration and the treatment arena. These include 1) home-administration managed by municipalities, 2) self-administration managed by hospitals and 3) treatment in local care facilities managed by either municipalities or hospitals. Compared to the international organisation of OPAT, the field is less specialized in Denmark. Despite variation in the organisation of OPAT in Denmark, visitation, preparation, follow up, and completion of patient continuity of care generally occur alike in the five regions. However, the application of elastomeric pumps, self-administration, the delivery of medicine, and the practice of registration is not homogeneously performed currently. The regional co-operation agreements have shown to be of great importance in working with OPAT across sectors. In those regions, where no concrete co-operation agreement concerning OPAT is available, there is a great wish for an agreement. Within the regional co-operation agreements and the national clinical guidelines, a framework of training and competency development amongst nurses managing OPAT is included. The perceived need of training and competency development amongst municipal nurses, however, varies. There can be different divisions of labour internally at the hospitals and in the municipalities in relation to OPAT treatment. However, there is a general agreement about the delegation of responsibilities (e.g. the medical treatment responsibility) between regions and municipalities, in cases where municipalities are involved.

According to the interview informants, challenges regarding OPAT include e.g. an increased burden of labour especially in the preliminary phase of OPAT and in the continuous monitoring of patients. Furthermore, some municipalities only have limited resources to manage OPAT care trajectories due to the fact that it is a comprehensive task for nurses to visit patients 3-4 times a day. Moreover, coordination and communication is an important precondition for OPAT, however, it can give rise to certain challenges, because of the involvement of many health professionals. According to the interview informants, with OPAT, nursing resources at the hospital can be freed, and the cross-sectional co-operation between involved professionals is strengthened. A

consensus amongst the interview informants of whether OPAT is resource-demanding or resource saving lacks. As regards potentials, the interview informants see great potential in moving more types of treatment from the hospital to patients' homes or in the community. Also potentials are seen in the application of pumps, and more specialised centres at the hospitals, that manage IV treatment, as seen in other countries. This can potentially give the area of OPAT a competency boost.

Costs and Economic Evaluation (ECO)

28 studies were included in the systematic review on economy. Reduction in costs comparing OPAT to IPAT was found in all included original studies and appeared to be consistent within the different patient groups and for various OPAT delivery models. Considering the effectiveness OPAT was generally found to be as effective or more effective than IPAT in the included outcomes. Thus, as OPAT was found to be less expensive and more effective than IPAT, the new strategy (OPAT) dominates the old one (IPAT).

The results of the economic literature may have limited transferability to the Danish setting, as financial structure and organisation of the health care system differ among countries. However, the consistent results showing that OPAT incurs cost savings imply that cost savings could be expected in the Danish setting as well, although the magnitude of the savings may be highly dependent on local organisation and delivery of the services.

With the aims of investigating the cost differences in a Danish setting to better inform local decision making, we performed a complimentary micro-costing analysis informed through interviews with clinical experts. Findings from the micro-costing analysis using different diagnostic cases supported the overall conclusion from the literature review; that OPAT care models were associated with a reduction in treatment costs. Not surprisingly care models with less need for health care services and support by health care staff showed the largest cost reductions compared to hospitalisation.

It must be noted that the cost-differences presented in the micro-costing are analytical calculations and should not be used in comparing the different models of care, as the different models are unlikely to be suitable for the same patients. Thus the different OPAT-models address a range of different patient needs from the possibility to continue the everyday life at home during treatment to the possibility of offering protected and individual care in a quiet and familiar environment. Hence the investigation of OPAT-models made it clear that there is no "one-fits-all" solution and choice of care model should be based on careful visitation taking into account the specific patients' needs and resources.

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APPENDIX 1. EXAMPLE SEARCH TERMS – PUBMED SEARCH

	Søgeord
#1	"Administration, Intravenous"[Mesh] OR "Infusions, Parenteral"[Mesh]
#2	Intravenous OR parenteral
#3	#1 OR #2
#4	"Anti-Bacterial Agents"[Mesh]
#5	antimicrobial OR antibiotic* OR antibacterial
#6	#4 OR#5
#7	"Outpatients"[Mesh] OR "Ambulatory Care"[Mesh] OR "Home Infusion Therapy"[Mesh]
#8	out-of-hospital OR home OR outpatient* OR self-administered
#9	#7 OR #8
#10	#3 AND #& AND #9
#11	OPAT OR S-OPAT OR OHPAT
#12	#9 OR 10

APPENDIX 2: INVITED AND PARTICIPATING INFORMANTS IN INTERVIEWS, ORGANISATIONAL ASPECTS

Region	Institution	Administrative employee/leader	Physician	Nurse
Region of Southern Denmark	Central Administration	x		
	Odense Universitetshospital		x	x
	Sønderborg Kommune	x		x
	Odense Kommune	x		x
Central Denmark Region	Central Administration	x		
	Aarhus Universitetshospital		o	x
	Unspecified municipality	o		o
North Denmark Region	Central Administration	x		
	Aalborg Universitetshospital		x	o
	Mariagerfjord Kommune	x		
The Capital Region	Central Administration	x		
	Nordsjællands Hospital		x	x
	Hillerød Kommune	x		x
	Frederikssund Kommune	x		x
The Zealand Region	Central Administration	x		
	Nykøbing Falster Sygehus		x	x
	Unspecified municipality			
x indicates participation in interview.				
o indicates invited for participation but no participation in interview.				
Empty space indicates not invited for participation in interview				

APPENDIX 3: INTERVIEW GUIDES, ORGANISATIONAL ASPECTS

Interviewguide – Regionale stabsmedarbejdere
Baggrund
Hvor mange hospitaler og kommuner i jeres region indgår i aftaler om IV-behandling uden for hospitalet? (samme aftale / forskellige aftaler?)
Har I et overblik over omfanget af patienter i regionen der sendes hjem til IV-behandling uden for hospitalet?
Organisering
Hvordan er IV-behandling uden for hospitalet overordnet organiseret i jeres region? (fx i forhold til organisatorisk forankring, ansvarsfordeling, beslutningsprocesser).
Hvilken rolle spiller I som region i patientforløb for patienter med IV-behandling uden for hospitalet? (fx ift. igangsætning, koordinering, løbende opfølgning, afslutning og regulering af forløb)
Hvordan foregår afregningen mellem sygehuse/regioner og kommuner? /Hvordan kunne det foregå?
Hvordan fastsættes takster for hjemmebehandling? /Hvordan kunne de evt. fastsættes?
Hvordan er organiseringen af IV-behandling uden for hospitalet aktuelt reguleret i regionen? (fx retningslinjer, samarbejdsaftaler)
Foregår der sparring/samarbejde på tværs af regioner om behandling af patientgruppen?
Hvad er formålet og baggrunden for udarbejdelsen af samarbejdsaftalerne?
Har der været tværregional sparring eller samarbejde i forbindelse med udarbejdelsen af samarbejdsaftalerne?
Foregår der løbende monitorering og kvalitetssikring af IV-behandling uden for hospitalet i jeres region – i så fald: hvordan?
Samarbejde
Hvordan oplever I, at samarbejdet mellem hospitaler og kommuner fungerer omkring IV-behandling uden for hospitalet?
Spiller almen praksis en rolle i forhold til IV-behandling uden for hospitalet? (hvis ja, hvilken?)
Vurdering og fremadrettede perspektiver
Hvilke potentialer eller muligheder ser I ved den aktuelle organisering af IV-behandling uden for hospitalet?
Hvilke udfordringer ser I ved anvendelsen af IV-behandling uden for hospitalet ved den nuværende organisering?
Hvilke fordele/ulemper ser I ved den kapacitetsfrigivelse, der kommer ved at flytte behandlingen hjem i stedet for at det varetages på hospitalet
Hvilke forslag til fremadrettede ændringer/forbedringer har I i forhold til håndtering og organisering af IV-behandling uden for hospitalet?
På hvilke niveauer foregår beslutningstagning i forhold til ændring/forbedring af organisering af IV-behandling uden for hospitalet?

Interviewguide – Læger og sygeplejersker på hospital
Baggrund
Hvor mange patienter pr. måned (gennemsnitligt) bliver visiteret til IV-behandling uden for hospitalet i jeres afdeling?
Hvilke typer af patienter bliver typisk visiteret til IV-behandling uden for hospitalet? /Hvilke overvejelser ligger bag?
Hvad er den typiske varighed behandlingsforløb (gennemsnitligt) for de forskellige patienter/diagnoser?
Organisering
Kan I beskrive, hvordan visitation af patienter til IV-behandling uden for hospitalet foregår?
Hvilke forskellige modeller findes til IV-behandling uden for hospitalet? Hvordan vurderes hvilket tilbud der er mest relevant?
Kan I beskrive hvordan et typisk patientforløb ser ud fra beslutning om IV-behandling er taget til denne er i gang og afsluttet?
Hvilken rolle spiller I som hhv. læge og sygeplejerske (på hospitalet) i patientforløbets forskellige faser?
Har I fået 'nye' opgaver i forbindelse med hjemsendelse af patienterne?
Hvad er de væsentligste organisatoriske såvel som personalemæssige forudsætninger for at behandlingen kan fungere? (fx samarbejdsaftaler, uddannelse af personale)
Hvilken oplæring/kompetencer er nødvendige i fht. varetagelse af IV-behandling uden for hospitalet? Hvem faciliterer oplæringen?
Foregår der løbende monitorering og kvalitetssikring af IV-behandling uden for hospitalet i jeres region – i så fald: hvordan?
Samarbejde og koordinering
Hvordan ser I hospitalets/regionens rolle og ansvarsområde i forbindelse med IV-behandling uden for hospitalet?
Hvordan ser I kommunens rolle og ansvarsområde i forbindelse med IV-behandling uden for hospitalet? Har almen praksis en rolle?
På hvilke tidspunkter i patientforløbet er der som oftest behov for afklaring og kommunikation mellem de forskellige involverede parter i behandling?
Er der etableret strukturer eller initiativer, som faciliterer samarbejdet? (fx fora hvori man modes, samarbejdsaftaler, retningslinjer – formaliseret eller uformelt?)
Hvad betyder samarbejdsaftalen for jeres arbejde? /Savner I en regional samarbejdsaftale mellem hospitaler og kommuner?
Hvordan fungerer samarbejdet mellem hospital og kommune?
Vurdering og fremadrettet organisering
Hvilke potentialer eller muligheder ser I ved den aktuelle organisering af IV -behandling uden for hospitalet?
Hvilke udfordringer ser I ved anvendelsen af IV-behandling uden for hospitalet ved den nuværende organisering?
Hvilke forslag til fremadrettede ændringer/forbedringer har I i forhold til håndtering og organisering af IV-behandling uden for hospitalet?

Interviewguide – Kommunale ledere/stabsansatte og hjemmesygeplejersker

Baggrund

Hvor mange patienter pr. måned (gennemsnitligt) bliver visiteret til IV-behandling uden for hospitalet i jeres kommune?

Hvilke typer af patienter bliver typisk visiteret til IV-behandling uden for hospitalet? /Hvilke overvejelser ligger bag?

Hvad er den typiske varighed af et behandlingsforløb (gennemsnitligt) for de forskellige patienter/diagnoser?

Organisering

Kan I fortælle, hvordan organiseringen af IV-behandling uden for hospitalet ser ud i jeres kommune? (Fx i forhold til organisatorisk forankring, forskellige modeller, personale, ansvarsfordeling)

Hvordan er sammensætningen af faggrupper, der varetager IV-behandlingen?

Kan IV-behandlingen varetages i forbindelse med andre aktiviteter hos patienten?

Kan I beskrive hvordan et typisk patientforløb ser ud fra beslutning om IV-behandling er taget til denne er i gang og afsluttet?

Hvilke 'nye' opgaver varetages af kommunalt personale i forbindelse med IV-behandling uden for hospitalet?

Hvad er de væsentligste organisatoriske såvel som personalemæssige forudsætninger for at behandlingen kan fungere? (fx samarbejdsaftaler, uddannelse af personale)

Hvilken oplæring/kompetencer er nødvendige i fht. varetagelse af IV-behandling uden for hospitalet? Hvem faciliterer oplæringen?

Foregår der løbende monitorering og kvalitetssikring af IV-behandling uden for hospitalet i jeres kommune – i så fald: hvordan?

Samarbejde og koordinering

Hvordan ser I kommunens rolle og ansvarsområde i forbindelse med IV-behandling uden for hospitalet? Har almen praksis en rolle?

Hvordan ser I hospitalets/regionens rolle og ansvarsområde i forbindelse med IV-behandling uden for hospitalet?

På hvilke tidspunkter i patientforløbet er der som oftest behov for afklaring og kommunikation mellem de forskellige involverede parter i behandling?

Er der etableret strukturer eller initiativer, som faciliterer samarbejdet? (fx fora hvori man modes, samarbejdsaftaler, retningslinjer)

Hvad betyder samarbejdsaftalen for jeres arbejde? /Savner I en regional samarbejdsaftale mellem hospitaler og kommuner?

Hvordan fungerer samarbejdet mellem hospital og kommune?

Vurdering og fremadrettet organisering

Hvilke potentialer eller muligheder ser I ved den aktuelle organisering af IV -behandling uden for hospitalet?

Hvilke udfordringer ser I ved anvendelsen af IV-behandling uden for hospitalet ved den nuværende organisering?

Hvilke forslag til fremadrettede ændringer/forbedringer har I i forhold til håndtering og organisering af IV-behandling uden for hospitalet?

APPENDIX 4: CHARACTERISTICS OF INCLUDED STUDIES, ORGANISATIONAL ASPECTS

Study	Aim	Study design and methods	Results	Quality
Chapman et al., 2012, United Kingdom	To develop a set of consistent, usable, UK-wide, good practice recommendations ensuring the provision of an equivalent quality of care, the maximization of patient benefits and the minimization of clinical risk.	Literature review	The revised good practice guidelines provide pragmatic guidance on the development and delivery of OPAT services. The guidelines focus on the following areas relevant to OPAT; the OPAT team and service structure; patient selection; antimicrobial management and drug delivery; monitoring of the patient during OPAT; outcome monitoring and clinical governance.	No quality assessment performed because of study design
Bowling et al., 2013, United States	To describe central elements within OPAT services	Expert assessment	Considerations reflected in the article include patient selection, current practice guidelines, the OPAT team, antibiotic choices, adverse events, and monitoring outcomes	No quality assessment performed because of study design
Muldoon et al., 2013, United States	To review 6 components that are believed to comprise an OPAT bundle, which is a set of OPAT-specific practices. The literature review examines the current literature supporting each component.	Literature review	The proposed OPAT bundle consists of 6 main bundle components, including patient identification/selection, infectious disease consultation, patient/family education, care transition, outpatient monitoring, and OPAT program measures. In the light of the above, evidence base is lacking in each of the 6 identified components, particularly in the areas of patient education and care transition.	No quality assessment performed because of study design
Nazarko, 2013, United Kingdom	To examine service models, that set up services and develop staff to enable them to deliver OPAT services	Expert assessment	There are three ways to deliver OPAT, including self-administered OPAT, OPAT delivered in infusion centers, and staff delivered home-based services. A range of IV therapies can be delivered outside of hospitals, e.g. antimicrobials, chemotherapy, and IV fluids. OPAT is best managed and delivered by a team, which normally consists of a physician with expertise in antibiotic therapy e.g. an infectious disease consultant. Furthermore, the team should have specialist nursing and community nursing input. Staff requires training to ensure that they have adequate theoretical and practical skills and competencies to carry out IV therapy in the community. Furthermore, staff shall have access to nurse specialist support and support of the OPAT team.	No quality assessment performed because of study design
Norris et al., 2019, United States	A panel of experts was convened by the Infectious Diseases Society of America (IDSA) to update the 2004 clinical practice guideline on outpatient parenteral antibiotic therapy (OPAT).	Literature review and 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE)	The guideline is intended to provide insight for healthcare professionals who prescribe and oversee the provision of OPAT. Best practice tables that address pharmacokinetic features, administration options, and potential adverse effects of selected antimicrobials are included in the guideline. Recommendations are offered in the areas of: patient considerations, antimicrobial utilization, vascular access devices, monitoring, and antimicrobial stewardship.	No quality assessment performed because of study design
Romo et al., 2013, United States	To identify and describe key elements vital to establish an OPAT program	Expert assessment	In order to establish a successful OPAT program adequate patient selection, a structured OPAT team with an effective communication system, and routine clinical monitoring are considered key elements.	No quality assessment performed because of study design

Study	Aim	Study design and methods	Results	Quality
Seaton et al., 2013, United Kingdom	To identify and describe key principles and practises within OPAT services	Literature review	Results indicate that OPAT is a cost-effective mode of care for a variety of different infectious diseases, and that different OPAT models outside the hospital exist. Elements that are vital to consider within an OPAT program include; the OPAT team and service structure; OPAT patient selection; antimicrobial management and drug delivery; intravascular devices and administration of antimicrobial; clinical monitoring of the patient; and economics of the OPAT service.	No quality assessment performed because of study design
Halilovic et al., 2014, United States	To examine some of the most common challenges in the process of starting up and managing an OPAT program. Furthermore, the review gives practical advice on addressing the identified common issues	Literature review	Overall, 6 challenges regarding respectively the OPAT team and the creation of a safe and effective treatment plan have been identified and examined while possible solutions to these challenges have been assessed. The identified challenges concern; the selection of the OPAT team members and the determination of whether a patient is an appropriate candidate for OPAT; the existing options for parenteral antimicrobial infusion outside the hospital; the devising of a treatment regimen that is clinically sound and has low risk of complications; the minimizing of complications and the ensuring of safe OPAT administration; the avoidance of delays in OPAT care; and the addressing of funding issues for OPAT	No quality assessment performed because of study design
Patel et al., 2015, United Kingdom	To develop good practice recommendations to ensure good clinical practice and governance within pediatric OPAT (p-OPAT) services across the UK	Literature review	The good practice recommendations provide a practical approach for a safe delivery of p-OPAT services in secondary and tertiary care settings. The recommendations have been divided into eight key areas. These address respectively roles and responsibilities of the p-OPAT team, structure required to deliver the service, the identification of patients and pathologies that are suitable for p-OPAT, and the ensuring of appropriate vascular access. They also concern antimicrobial selection and delivery, the clinical aspects of delivering p-OPAT services, and the process of writing a business case supporting the introduction of a p-OPAT service.	No quality assessment performed because of study design
Bellamy, 2018, United Kingdom	To describe the different types of OPAT that exist, and the patients who can be treated. Furthermore, the review aims to examine the standards that a good OPAT service should achieve and potential benefits.	Literature review	Three general delivery systems of OPAT exists, including outpatient (patient attends a clinic in a hospital or community setting), home administration (IV antibiotics is administered by a specialist or a general district nurse), and self-administration (the patient administer the IV antibiotics him/herself). Patients who receive OPAT include patients with conditions such as cellulitis, osteomyelitis, septic arthritis, endocarditis, pneumonia, lung abscess, meningitis, and intravenous line infections. Circumstances vital to consider to ensure safe and effective care involve structure of the OPAT service, patient selection, antimicrobial management, patient monitoring, and clinical governance	No quality assessment performed because of study design
Steffens et al., 2019, Belgium	To describe barriers of OPAT at home	Literature review	The implementation of ABS guidelines in OPAT programs, e.g. by using a multidisciplinary team approach and facility specific protocols for OPAT with patient selection criteria and instructions for selection, storage, preparation and administration of antibiotics, can improve appropriate antibiotic use.	No quality assessment performed because of study design

Study	Aim	Study design and methods	Results	Quality
Berrevoets et al., 2020, Netherlands	To develop a set of quality indicators that can be used to assess the appropriateness of outpatient parental antibiotic therapy (OPAT) care	Literature review	In agreement, 33 OPAT specific recommendations covering the entire OPAT pathway were carried out by an expert panel. The recommendations describe optimal OPAT care and can potentially serve as a framework for implementation. The presence of a structured OPAT program, a formal OPAT care team, and a treatment and monitoring plan is examples on quality indicators prioritized by the expert panel.	No quality assessment performed because of study design

APPENDIX 5: REGIONAL CO-OPERATION AGREEMENTS

Region	North Denmark Region	Central Denmark Region	The Region of Southern Denmark	Region of Zealand	Capital Region of Denmark
Document, year	Cooperation agreement regarding intravenous (IV) treatment within the framework of municipalities, 2020	IV treatment in the immediate environment – cooperation agreement within the health agreement, 2020	Cooperation agreement regarding IV treatment with antibiotics, 2017	Cooperation regarding transfer of tasks and delegation, 2014	Cooperation agreement regarding the municipal emergency functions in the Capital Region of Denmark, 2019
Varieties of treatment	IV treatment with antibiotics, fluids, and diuretic treatment	IV treatment with antibiotics, and isotonic fluids	IV treatment with antibiotics	The varieties of treatment is not clarified, however IV treatment with antibiotics is not mentioned	The varieties of treatment is not clarified, however IV treatment with antibiotics is not mentioned
Parties involved in the agreement	North Denmark Region and the North Jutland municipalities	Central Denmark Region and the Central Jutland municipalities	South Denmark Region and the municipalities of South Denmark	Region of Zealand and the municipalities within Region of Zealand	The PLO-capital, Capital Region of Denmark, and the municipalities within the Capital Region of Denmark
Aim of the agreement	The aim of the agreement is to give medical qualified patients the opportunity to receive IV within the framework of municipalities. Furthermore the agreement shall ensure that the transfer of tasks between sectors is planned and coordinated	The aim of the agreement is respectively to ensure that the continuity of care occurs on the terms of patients, to make treatment in the patients' immediate environment possible, and to ensure homogeneous execution of tasks across hospitals and municipalities for the benefit of patients	The aim of the agreement is to give medical qualified patients the opportunity to complete IV treatment with antibiotics at home or close to the patients' immediate environment, e.g. in a health centre	The aim of the agreement is to outline the transference of tasks and to ensure proper delegation of tasks and responsibilities between parties	The aim of the agreement is to ensure proper and high quality, patient safety, and coherence in the continuity of care in the municipal emergency function in the region of home nursing care

Target group	Patients above the age of 15 years Patients with acute or chronic infections	Patients above the age of 3 years	Medically stable patients receiving IV treatment with antibiotics that does not need hospitalization required treatment. Furthermore, the patients shall be considered suitable to complete the treatment at home	-	Doctor referred patients above the age of 18 years with acutely occurred somatic disease, or worsening of already existing disease with a need of observation, nursing, and/or treatment without the need of hospitalization Doctor referred patients above the age of 18 years who, after discharge from somatic hospital, still have a need of complex nursing and/or treatment that requires specific nursing competences which are presentin a municipal emergency function Patients above the age of 18 years with a home nurse referral where the need of feedback regarding practical help to assessment or intervention from the municipal emergency function is required
Division of responsibilities *Hospital, municipality, general practitioner, and patient/relative*	*Region/hospital* The responsibility concerning all medical procedures in the specific IV treatment lies within the operating doctor *Municipality* Municipalities have the responsibility of providing manpower in form of nurses with requisite skills and competences to carry out and manage IV specific tasks outside the hospital. It is required that nurses have adequate experience with the handling of IV medication, that they	*Region/hospital* The hospital and the ward in charge of the treatment have the medical responsibility of the IV treatment until the treatment has been completed. The responsibility includes the following: - To ensure ordination of the most optimal treatment and treatment type - To carry out a medical assessment determining whether a patient can be treated in the framework of municipalities - To contact municipalities for the purpose of arranging the further	*Region/hospital* The medical responsibility of treatment lies within the operating hospital ward. The responsibility includes the following: - To ensure that patients are informed of the hospital discharge and IV treatment verbally and in writing - To ensure ordination of relevant antibiotic treatment - To carry out an assessment determining whether a patient can be treated at home	*Region/hospital* The medical responsibility of the IV treatment lies within the operating doctor in charge of the specific treatment *Municipality* The municipal council has the responsibility of ensuring the availability of adequate instruction guidelines, and to ensure that staff within the municipality are qualified to undertake requisite tasks. Furthermore, municipalities must	The responsibility of treatment lies within the doctor that has referred the patient to the municipal emergency function (it can potentially be the general practitioner)

	have received education to independently handle IV medication, or have received peer-to-peer training *General practitioner* The general practitioner has no responsibility for the ordinated IV treatment following hospital discharge	continuity of care within the municipality - To carry out an individual treatment plan, including a plan of control, follow up, and completion of treatment - To update the shared medicine journal including dose, daily number of doses, number of days of treatment, and discontinuation of IV treatment - To inform patients or/and relatives about the ordinated IV treatment - To provide municipal nurses in charge of medicine administration with sufficient advice - To deliver medicine and nurse specific commodities to the ordinated treatment *Municipality* Municipalities have the responsibility of educating municipal nurses in intravenous administration of medicine, and providing them with adequate competences. Furthermore, municipalities are responsible of conforming to the ordinated treatment, and to make sure that municipal nurses follows municipal instructions concerning anaphylactic shock treatment *General practitioner* The general practitioner has no responsibility for the ordinated IV treatment following hospital discharge	- To carry out a treatment plan, including end of treatment/moving to another administrative type etc. - To ensure that present ordinations and changes are updated and send to the municipality and the general practitioner - To establish a 24/7 hotline through which the hospital ward can give municipal nurses advice *Municipality* IV treatment with antibiotics is defined as a "can-job" in the Danish Health Authority's standards of quality for municipal emergency functions in home nursing *General practitioner* After the completion of IV treatment and in the event of diseases that are not related to the specific IV treatment, the responsibility lies within the general practitioner	supervise executed tasks. *General practitioner* -	
Visitation *Who carry out the assessment of eligibility?*	-	Completion of IV treatment in the local environment of a patient requires an assessment of the patient's eligibility, and the patient's home address must be assessed for eligibility by the home nurse. Furthermore, the patient's course	The patient's home address must be eligible for the introduction of IV treatment. The assessment assessing the eligibility of the patient's home		General practitioners, doctors in 1813, and doctors at the hospital are able to refer patients to the municipal emergency function, if the patient fits into the target group, and if the patient needs

		of treatment must be medically stable The overall assessment of the patient's eligibility occurs within a cooperation between the patient, patient relatives, municipal and regional health professionals	address is based on a dialogue between the patient and the involved, municipal nurse		the emergency function's provided treatments The municipal emergency function has the visitation right. Thus, the emergency function assesses whether the continuation of care can be managed in the emergency function.
Training and education	Transfer of tasks requires competency development among municipal nurses for the purpose of ensuring the applying of existing guidelines regarding hygiene, observation, care of IV access, exemption and administration of IV medicine, observation of effects and side effects Educators within the hospital educate municipal nurses in essential treatment procedures. Furthermore, they demonstrate and provide municipal nurses with utensils in the educational lessons The hospital pays educators, while municipalities pay the education specific facilities, the scheduling and holding of nurses' teaching. Jointly, hospitals and municipalities arrange how competency development is executed within the municipality to ensure that municipal nurses are able to perform the required procedures and treatments.	Competencies required among municipal nurses concerning IV treatment include the following: - Administration of medicine in PVK, PICCline, VIP, CVK, MIDline - Application of elastomeric pump and Codanmix add set - Observation of effects and side effects (e.g. allergic reactions) - Initiation of treatment of anaphylactic shock. Locally in the clusters, it is arranged how municipal nurses' possibility of relevant competency development regarding the performance of IV treatment is ensured.	Competencies within the following areas is required in order to administer IV treatment with antibiotics: - Pharmacology, e.g. knowledge concerning effects, side effects, and interactions - Knowledge and primary treatment of allergic reactions, e.g. anaphylactic shock - IV access care - Observation of injection area and prevention of complications - Competencies concerning resuscitation The competency development is offered and coordinated locally in the local co-ordination forum	-	-
Monitoring	A steering committee has been established with the aim of ensuring follow-up on the regional cooperation agreement	It is being clarified within the IV group how the following shall be monitored - Continuous activity concerning estimated duration of number of courses and economy	Continuous monitoring on municipal/regional level of the following: - Number of citizens referred to IV treatment with antibiotics	-	To establish a sustainable foundation for the planning, follow up, and quality development of the cooperation, the intervention in the municipal emergency functions must be monitored. On

		- Whether additional requisites last, including number of treatment days, number of doses per day etc. A survey regarding citizens' perception of the intervention's quality through questionnaires or interviews shall be executed. It shall cover whether the expected advantages are met. The questionnaire is accomplished by the municipalities within the region	- Average duration of treatment - Number of ordinating hospital wards - Number of citizens with complications		behalf of the committee of practice plan, a concrete proposal concerning the design, follow up, and monitoring of the agreement is being formulated An agreement concerning a joint experimental scheme with remuneration of general practitioners regarding communication/counselling about citizens in the emergency function has been signed.

APPENDIX 6: STUDIES IN THE INCLUDED REVIEWS, ECONOMY

Studies	Year	Balaguer & Gonzalez de Dios 2015(75)	Shepperd et al. 2016(76)	Mitchell et al. 2017(22)	Polinski et al. 2017(24)	Psaltidikis et al. 2017(25)	Bryant & Katz 2018(77)	Boese et al. 2019(78)	Included in this HTA 2020
Antoniskis et al.	1978					x		x	
Stiver et al.	1982					x			
Eisenberg et al.	1986					x			
Donati et al.	1987						x		
Chamberlain et al.	1988					x			
Grizzard et al.	1991							x	
Stovroff et al.	1994						x		
Hindes et al.	1995					x			
Grayson et al.	1995				x	x			
Graf von der Schulenburg et al.	1997					x			
Wolter et al.	1997	x			x				
Warner et al.	1998						x		
Jones et al.	1999		x						
Nathwani et al.	1999					x			
Wai et al.	2000					x		x	
Board et al.	2000		x						
Dalavisio et al.	2000					x			
Fishman et al.	2000						x		
Nicholson et al.	2001		x						
Steinmetz et al.	2001					x			
Bernard et al.	2001					x		x	
Remonnay et al.	2002				x				
Nathwani et al.	2003							x	
Raisch et al.	2003						x		
Krauth et al.	2003			x					
Patel et al.	2004		x						
Ricauda et al.	2004		x						

Wolter et al.	2004					x				
Richards et al.	2005		x							
Thornton et al.	2005			x						
Fisher et al.	2006					x				
Patanwala et al.	2007			x						
You et al.	2007			x						
Ricauda et al.	2008		x							
Chapman et al.	2009					x			x	
Yong et al.	2009				x	x			x	
Kieran et al.	2009					x			x	
Mendoza et al	2009		x							
Nguyen et al.	2010								x	
Heintz et al.	2011					x			x	
Lavie et al.	2011							x		
Teuffel et al.	2011			x		x				x
Gray et al.	2012								x	
Theocharis et al.	2012					x			x	x
Semple L.	2012					x				
Al Ansari et al.	2013					x				x
Lai et al.	2013					x				
Sims et al.	2013					x			x	
Lacroix et al.	2014					x			x	x
Revankar et al.	2014					x				
Seaton et al.	2014					x			x	
Al Alawi et al.	2015								x	
Ektare et al.	2015					x				
Harrison et al.	2015								x	
Hatziagorou et al.	2015							x		
Malone et al.	2015					x			x	x
Ruh et al.	2015					x			x	x
Subedi et al.	2015					x				
Beieler et al.	2016					x				
Hernandez et al.	2016					x				
Kameshwar et al.	2016					x				x

Peña et al.	2016		x		
Connors et al.	2017			x	x
Gonzales et al.	2017			x	x
Hensey et al.	2017			x	x
▪ **Additional in this HTA**					
Teuffel et al.	2011				x
Hendricks et al.	2011				x
Rodriguez-Cerillo et al.	2013				x
Chrysochoou et al.	2016				x
Ibrahim et al.	2017				x
Parajon et al.	2017				x
Burkett et al.	2018				x
Durojaiye et al.	2018				x
Ramasubramanian et al.	2018				x
Psaltidikis et al.	2018				x
Ibrahim et al.	2019				x

APPENDIX 7: CHARACTERISTICS OF INCLUDED SYSTEMATIC REVIEWS, ECONOMY

Author(s), publication year	Aim	Methods	Results	Declaration of interest	Funding source	Quality based on AMSTAR checklist
Balaguer & Gonzales, 2012	To determine whether home intravenous antibiotic therapy in cystic fibrosis is as effective as inpatient intravenous antibiotic therapy and if it is preferred by individuals or families or both.	Review type: Systematic review Search engines: Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register and hand searches	Eighteen studies were identified, but only one study could be included which reported results from 17 participants aged 10 to 41 years with an infective exacerbation of *Pseudomonas aeruginosa*. Home participants underwent fewer investigations than hospital participants ($P < 0.002$) and general activity was higher in the home group. No significant differences were found for clinical outcomes, adverse events, complications or change of intravenous lines, or time to next admission. Home therapy was cheaper for families and the hospital. Indirect costs were not determined.	Reported	Reported	Moderate quality

Author(s), publication year	Aim	Methods	Results	Declaration of interest	Funding source	Quality based on AMSTAR checklist
Shepperd et al., 2016	To determine the effectiveness and cost of managing patients with admission avoidance hospital at home compared with inpatient hospital care.	Review type: A systematic review and meta-analysis Search engines: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, EconLit and two trials registers	16 randomised controlled trials were included. Admission avoidance hospital at home probably makes little or no difference on mortality at six months' follow-up (risk ratio (RR) 0.77, P = 0.04;), little or no difference on the likelihood of being transferred (or readmitted) to hospital (RR 0.98, P = 0.84), and may reduce the likelihood of living in residential care at six months' follow-up (RR 0.35, P < 0.0001). Satisfaction with healthcare received may be improved with admission avoidance hospital at home; few studies reported the effect on caregivers. When the costs of informal care were excluded, admission avoidance hospital at home may be less expensive than admission to an acute hospital; there was variation in the reduction of hospital length of stay, estimates ranged from a mean difference of -8.09 days (95% CI -14.34 to -1.85) in a trial recruiting older people with varied health problems, to a mean increase of 15.90 days (95% CI 8.10 to 23.70) in a study that recruited patients recovering from a stroke.	Reported	Reported	High quality

Author(s), publication year	Aim	Methods	Results	Declaration of interest	Funding source	Quality based on AMSTAR checklist
Bryant & Katz, 2017	To review the efficacy, safety, satisfaction, and cost of home-based versus hospital-based intravenous antibiotic therapy for acute infections in children	Review type: A systematic literature review Search engines: MEDLINE and Embase	19 studies were included in the systematic review. No studies showed that home-based treatment was less safe than hospital-based treatment. In all studies in which treatment satisfaction or costs were assessed, home-based treatment was satisfactory to patients or patients' families and less expensive per episode than hospital-based treatment by 30–75%. Thus, home-based intravenous antibiotic therapy might be popular and cost-effective, but randomised studies of the efficacy of this strategy are needed.	Reported	Reported	Moderate quality
Mitchell et al. 2017	To evaluate evidence of the efficacy, safety, acceptability and cost-effectiveness of outpatient parenteral antibiotic therapy (OPAT) models.	Review type: A systematic review Search engines: MEDLINE, EMBASE, CINAHL, Cochrane Library, National Health Service (NHS), Economic Evaluation Database (EED), Research Papers in Economics (RePEc), Tufts Cost-Effectiveness Analysis (CEA) Registry, Health Business Elite, Health Information Management Consortium (HMIC), Web of Science Proceedings, International Pharmaceutical Abstracts, British Society for Antimicrobial Chemotherapy website.	29 studies involved a comparator. There was little difference in duration of OPAT treatment compared with inpatient therapy, and overall OPAT appeared to produce superior cure/improvement rates. Drug side effects, deaths and hospital readmissions were similar to those for inpatient treatment, but there were more line-related complications. Patient satisfaction was high, with advantages seen in being able to resume daily activities and having greater freedom and control.	Reported	Reported	Moderate quality

Author(s), publication year	Aim	Methods	Results	Declaration of interest	Funding source	Quality based on AMSTAR checklist
Polinski et al., 2017	To understand the utility of home infusion versus medical-setting infusion as a mechanism to affect the three-part aim: better care, better health outcomes and lower costs.	Review type: A systematic review Search engines: MEDLINE, EMBASE, and Science Citation Index	As compared to medical setting infusion patients, home infusion patients were no more likely to experience adverse drug events or side effects. Clinical outcomes were as good or better, e.g., for patients with hemophilia, a 40% (0.50–0.70) reduced likelihood of hospitalization for bleeding complications. Patients overwhelmingly preferred home infusion, reporting significantly better physical and mental wellbeing and less disruption of family and personal responsibilities. Home infusion costs were significantly lower than medical setting infusion costs, with savings between $1928 and $2974 per treatment course.	Reported	Reported	Moderate quality
Psaltikidis et al., 2017	To compare OPAT and hospitalization as health care modalities from an economic perspective.	Review type: A systematic review Search engines: Medline (via PubMed), PubMed, Embase, the Cochrane Library, Centre for Reviews and Dissemination (CRD), Lilacs, Bireme, Medscape, Trip database, Web of Science, INATHA, and grey literature	The study observed high heterogeneity in the following: countries, infection site, OPAT strategies and outcomes analysed. With respect to economic analyses, 71% of the studies considered the cost-consequences, 11% cost minimization, 6% cost-benefit, 6% cost-utility analyses and 6% cost effectiveness. Considering all 35 studies, the general OPAT cost saving was 57.19% (from −13.03% to 95.47%). Taking into consideration only high-quality studies (6 comparative studies), the cost saving declined by 16.54% (from −13.03% to 46.86%).	Reported	Reported	Moderate quality

APPENDIX 8: CHARACTERISTICS OF INCLUDED ORIGINAL STUDIES, ECONOMY

Study (author, year, country)	Aim	Methods	Results (Costs)	Declaration of interest	Funding source	Quality based on Drummond checklist
Hendriks et al., 2011, USA	To conduct an economic analysis of direct and indirect costs for inpatient versus early discharge to outpatient treatment of febrile neutropenia for low-risk patients with cancer.	Design: randomized trial Participants: adult cancer patients with febrile neutropenia (FN), 57 inpatient and 35 outpatient treatment episodes of patients. Intervention: home care versus hospital care Time frame: 1996 through 2000. Outcomes: direct medical and self-reported indirect costs	Mean total charges for the hospital arm were 49% higher than for the home treatment arm ($16,341 *v* $10,977). Mean estimated total costs for the hospital arm were 30% higher ($10,143 *v* $7,830). Inpatients and their caregivers spent more out of pocket than their outpatient counterparts (mean, $201 *v* $74). Informal caregivers for both treatment arms reported similar time caring and lost from work.	Reported	Not reported	8
Teuffel et al., 2011, Canada	To examine costs and effectiveness (measured as quality-adjusted FN episodes [QAFNEs]) of 4 different treatment strategies for low-risk FN	Design: a cost-utility model Participants: Adult cancer patients with low risk febrile neutropenia (FN) Intervention: 4 different strategies for low risk FN Time frame: average treatment duration (6 days) Outcomes: quality adjusted FN episodes (QAFNEs), costs (Canadian dollars), and incremental cost-effectiveness ratios	HomePO was cost saving ($3470 vs $4183), but less effective (0.65 QAFNE vs 0.72 QAFNE) than HomeIV. The corresponding ICER was $10 186 per QAFNE. Both EarlyDC ($6115; 0.66 QAFNE) and HospIV ($13 557; 0.62 QAFNE) were dominated strategies. At a willingness-to-pay (WTP) threshold of $4 000 per QAFNE, HomePO and HomeIV were cost effective in 54 and 38% of simulations, respectively.	Reported	Reported	10

Study (author, year, country)	Aim	Methods	Results (Costs)	Declaration of interest	Funding source	Quality based on Drummond checklist
Teuffel et al., 2011 [2], Canada	To examine costs and effectiveness (measured as quality-adjusted FN episodes [QAFNEs]) of 4 different treatment strategies for low-risk FN	Design: a cost-utility model Participants: paediatric patients with cancer Intervention: 4 different strategies for low risk febrile neutropenia (FN) Time frame: average treatment duration (6 days) Outcomes: quality adjusted FN episodes (QAFNEs), costs (Canadian dollars), and incremental cost-effectiveness ratios	The most cost-effective strategy was HomeIV. It was cost saving ($2732 vs $2757) and more effective (0.66 vs 0.55 QAFNE) as compared with HomePO. EarlyDC was slightly more effective (0.68 QAFNE) but significantly more expensive ($5579) than HomeIV, which resulted in an unacceptably high incremental cost-effectiveness ratio of more than $130 000 per QAFNE. HospIV was the least cost-effective strategy because it was more expensive and less effective than EarlyDC.	Reported	Reported	10
Theocharis et al., 2012, Greece	To present data from a Greek OPAT experience.	Design: retrospective study Participants: Adult patients, multiple diagnoses Intervention: OPAT delivered by SOS-staff Time frame: May 2009 to September 2010 Outcomes: Cure, mortality and costs	The mean cost per patient was €637 and was comparable to the mean cost if the patient were to be hospitalized for the same infection.	Reported	Reported	2

Study (author, year, country)	Aim	Methods	Results (Costs)	Declaration of interest	Funding source	Quality based on Drummond checklist
Al Ansari et al., 2013, Bahrain	To review the OPAT services and to explore patient satisfaction with the services provided, and to determine cost effectiveness	Design: retrospective study Participants: 101 patients who were treated at the OPAT clinic. Intervention: OPAT clinic, the OPAT clinic provides the same care and treatment on site as inpatient care without the need for an overnight hospital stay. Time frame: February 2012 to January 2013 Outcomes: Patient's satisfaction and costs	Cost was reduced from $75, 000 to $30, 000 over one year. This retrospective study suggested that OPAT service is safe and potentially a cost saving approach for the health care system.	Reported	Not reported	3
Rodriguez-Cerrillo et al., 2013, Spain	To compare the outcomes of elderly patients with uncomplicated diverticulitis who were treated at home versus traditional Hospitalization.	Design: prospective study Participants: patients over 70 years with uncomplicated diverticulitis Intervention: admission at Hospital at Home Unit versus Conventional Hospitalization Time frame: March 2011 to September 2012 Outcomes: patients characteristics and cost	Home treatment was associated with a cost reduction of 1368 euros per patient.	Reported	Not reported	2

Study (author, year, country)	Aim	Methods	Results (Costs)	Declaration of interest	Funding source	Quality based on Drummond checklist
Lacroix et al., 2014, France	To evaluate the benefit/risk ratio of outpatient parenteral antimicrobial therapy (OPAT) in infective endocarditis (IE).	Design: retrospective study Participants: adult patients with definite IE according to Duke criteria Intervention: OPAT Time frame: January 1 to December 30, 2012 Outcomes: demographic characteristic, comorbidities, diagnostic criteria for IE, adverse events observed during hospitalization and during the following 3 months and costs	The global saving was estimated at 267,307 euros, or 14,850 euros per patient.	Reported	Reported	4
Malone et al., 2015, Australia	To determine clinical outcomes in patients with diabetic foot infections receiving outpatient parenteral antimicrobial therapy (OPAT), to evaluate cost savings from the use of OPAT and to analyse demographic, clinical and laboratory data that may predict OPAT failure.	Design: retrospective cohort analysis Participants: Adult patients with diabetic foot infection Intervention: OPAT Time frame:1 January 2007 to 7 July 2012 Outcomes: clinical outcomes in patients with DFIs undergoing OPAT and costs	A total of 1569 days were saved by using outpatient parenteral antimicrobial therapy for an estimated total cost saving of $983 645 or $16 672 per patient	Reported	Not reported	3

Study (author, year, country)	Aim	Methods	Results (Costs)	Declaration of interest	Funding source	Quality based on Drummond checklist
Ruh et al., 2015, USA	To determine the outcomes (efficacy and adverse drug event complications) of a home intravenous antibiotic infusion program in a Veterans Affairs facility.	Design: a retrospective chart review Participants: Adult patients, multiple diagnoses Intervention: intravenous antibiotics at home Time frame: 2011 to 2013 Outcomes: readmission, dead, adverse drug events and cost	Compared with inpatient or rehabilitation care, the cost savings was $6,932,552.03 or $2,649,870.68, respectively.	Reported	Reported	6
Chrysochoou et al., 2016, Greece	To evaluate the safety and effectiveness of home IV antibiotic therapy compared to hospital therapy, among children with Cystic fibrosis (CF).	Design: prospective study design Participants: thirty-five stable paediatric patients with CF, chronically colonized with PsA Intervention: administering IV antibiotics at home versus hospital Time frame: January to December 2014. Outcomes: quality of life (QoL) and cost	There were no differences in baseline QoL scores between the hospital and home group. The cost of home IV therapy was significantly lower than the cost of hospital treatment (2100€ vs 3360€, respectively, p <0.001).	Reported	Not reported	4
Kameshwar et al., 2016, Australia	To compare hospital in the home (HITH) and ward-based management with respect to overall health service utilization by quantifying actual healthcare costs in a representative cohort of cellulitis patients, in a manner that controls for potentially confounding variables.	Design: retrospective cohort study Participants: Adult patients with ICD code of lower-leg cellulitis Intervention: admission at HITH versus hospital Time frame: 2012–13 Outcomes: length of stay (LOS) and individual clinical costing (ICC) between HITH- and non-HITH-treated patients	For 328 admissions of 294 patients, the average per-day costs were AU$431 for HITH and AU$761 for inpatient care. The LOS was higher for inpatient group. In multivariable analysis controlling for age, comorbidity, carer support and language, HITH remained associated with significantly longer LOS and non-significantly with higher cost.	Reported	Reported	6

Study (author, year, country)	Aim	Methods	Results (Costs)	Declaration of interest	Funding source	Quality based on Drummond checklist
Connors et al., 2017, Canada	Evaluation of Acute Dental Infections (ADI) referrals to a regional OPAT program in a large Canadian center	Design: Prospective study Participants: Adult patients with ADI Intervention: OPAT program that provides community-based parenteral antibiotic therapy seven days a week under the guidance of an infectious diseases physician for indicated infections following referral. Time frame: February to June 2014 Outcomes: Demographic and clinical outcomes and costs.	Conservative cost estimate of OPAT care was $120,096, a cost savings of $597,434 (83%) compared with hospitalization	Reported	Reported	6
Gonzalez-Ramallo et al., 2017, Spain	To assess the direct healthcare costs of outpatient parenteral antimicrobial therapy (OPAT) administered by Hospital at Home (HaH) units in Spain	Design: retrospective study Participants: patients who were treated at home by the OPAT units of three Spanish university hospitals Intervention: Hospital at Home (HaH), hospital-based and consists of physicians and nurses who monitor patients daily and make home visits Time frame: January 2012 to December 2013 Outcomes: Costs	The mean total cost of each infectious episode was €6707 [95% confidence interval (CI) €6189–7406]. The mean cost per OPAT episode was €1356 (95% CI €1247–1560), mainly distributed between healthcare staff costs (46%) and pharmacy costs (39%). The mean cost of inpatient hospitalisation of an infectious episode was €4357 (95% CI €3947–4977). The cost per day of inpatient hospitalisation was €519, whilst the cost per day of OPAT was €98, meaning a saving of 81%.	Reported	Reported	7

Study (author, year, country)	Aim	Methods	Results (Costs)	Declaration of interest	Funding source	Quality based on Drummond checklist
Hensey et al., 2017, Australia	To compare clinical characteristics and outcomes between hospital and home treatment and to identify factors influencing home treatment	Design: retrospective study Participants: children admitted to the hospital with pyelonephritis or proven and presumed bacterial meningitis Intervention: OPAT (home group) received daily visits via a Hospital-in-the-Home (HITH) program Time frame: January 1, 2012, to December 31, 2013 Outcomes: Clinical and demographic features, length of stay, readmission rate and cost	The average cost of OPAT via HITH versus an inpatient bed for medical patients is AU$210/day versus AU$800/day. Transfer to HITH resulted in a saving of AU$178,180	Not reported	Not reported	3
Ibrahim, 2017, Australia	To describe the characteristics of children treated via the direct-to-home from the ED pathway and to prospectively evaluate the outcomes of these children.	Design: prospective, observational cohort study Participants: Children aged 6 months–18 years attending the ED with uncomplicated moderate/severe cellulitis Intervention: intravenous ceftriaxone at home or intravenous flucloxacillin in hospital based on physician discretion. Time frame: March 2014–January 2015 Outcomes: treatment failure, duration of intravenous Antibiotics, complications and cost comparison	Home treatment costs less, averaging $A1166 (£705) per episode compared with $A2594 (£1570) in hospital.	Reported	Reported	4

Study (author, year, country)	Aim	Methods	Results (Costs)	Declaration of interest	Funding source	Quality based on Drummond checklist
Parajon et al., 2017, Spain	To evaluate the efficiency of treatment of infectious endocarditis (IE) via Self-administered Outpatient Parenteral Antimicrobial Therapy (S-OPAT) supported by a shortening hospital admission program in a hospitalization-at-home unit (HAH).	Design: retrospective study Participants: adult patients with infective endocarditis Intervention: OPAT delivered by HAH Time frame: 1988 to 2014 Outcomes: characteristics of each episode of IE, safety and efficiency of the care model, cost	The average cost of a day stay in HAH was €174 while in traditional cardiology hospitalization was €1100. The total average cost of treatment of each episode of IE managed entirely in hospital was calculated as €54,723.	Reported	Reported	4
Burkett et al., 2018, the US	To evaluate an OPAT program that treated community-acquired pneumonia.	Design: a medical record retrospective chart review Participants: adult patients with community-acquired pneumonia (CAP) Intervention: OPAT on-site at a medical center Time frame: September 2014 to December 2014 Outcomes: comorbidities, adverse drug events, LOS and cost	In addition to the cost of the drug, the total outpatient expenses for OPAT averaged $200 per day. This expense included all payment for supplies, staff, and billing charges for each patient. On average, the OPAT program will cost $600 for a 3-day treatment. It is estimated that an average cost of an inpatient hospitalization at a non-profit hospital in Pennsylvania is $2306 per day, and a 3-day inpatient hospital stay would cost $6918.26 This is a cost savings of $2106 per patient per day when OPAT is used.	Reported	Reported	5

Study (author, year, country)	Aim	Methods	Results (Costs)	Declaration of interest	Funding source	Quality based on Drummond checklist
Durojaiye et al., 2018, UK	To describe the OPAT service based in a large UK teaching hospital in Sheffield, and examine the clinical efficacy, patient acceptability and costs saved over a 10-year period.	Design: retrospective study Participants: patients >16 years, multiple diagnoses Intervention: OPAT service within a hospital run by a multi–disciplinary team. Antimicrobials are delivered by three distinct pathways: daily attendance at the infusion centre; self or carer administration in the patient's home; and administration by a district nurse in the patient's home. Time frame: 2006 to 2016 Outcomes: infection rate, readmission, cost, patient satisfaction	The total cost of the OPAT service over the 10-year period was £4,824,507 (i.e. £4,729,071 plus £95,436) at 2011–2012 prices. The total estimated costs of equivalent inpatient care for the 3812 patient episodes were £32,715,992 and £11,961,081, respectively. When the national average unit costs were used, the total estimated cost was £12,264,388. Using the minimum national unit costs within each diagnostic category, the total cost was £11,045,779	Reported	Reported	7
Psaltikidis et al, 2018, Brazil	To assess the cost-utility of OPAT in relation to inpatient parenteral antimicrobial therapy (IPAT),	Design: prospective study/model-based Participants: adult patients, multiple diagnoses Intervention: OPAT administered at an infusion center in a university hospital Time frame: 2015 to 2016 Outcomes: clinical outcomes, QALY and cost	OPAT compared to IPAT generated overall savings of 31.86% from the hospital perspective and 26.53% from the SUS perspective. The intervention reduced costs, with an incremental cost-utility ratio of −44,395.68/QALY for the hospital and −48,466.70/QALY for the SUS, with better cost-utility for treatment times greater than 14 days.	Reported	Reported	9

Study (author, year, country)	Aim	Methods	Results (Costs)	Declaration of interest	Funding source	Quality based on Drummond checklist
Ramasubramanian et al., 2018, India	To evaluate the clinical response of ertapenem in ESBL-positive APN. Secondary objective was to evaluate the cost comparison of ertapenem under OPAT versus inpatient settings.	Design: retrospective study Participants: adult patients with acute pyelonephritis Intervention: Hospital/OPAT or OPAT only Time frame: from 2010 to 2014 Outcomes: response to ertapenem and cost of treatment in inpatient versus OPAT settings	A significant reduction in treatment cost was seen in patients who received ertapenem as OPAT. Median charges at KIMS were hospital only (INR 133,510), hospital/OPAT (INR 81,716), and OPAT only (INR 17,718).	Reported	Reported	2
Ibrahim et al., 2019, Australia	To assess the cost-effectiveness of an admission avoidance pathway, in which children were treated at home, compared with standard hospital care for the intravenous treatment of moderate or severe cellulitis.	Design: cost-effectiveness analysis (based on RCT) Participants: children aged 6 months to 18 years with moderate or severe cellulitis Intervention: treatment at home under the Hospital-in-the-Home programme Time frame: January 2015 to June 2017 Outcomes: cost, QALY and treatment failure	The institutional cost per patient per episode was significantly lower in the home group than in the hospital group (AUS$1965 *vs* $3775; p<0·0001). The mean cost incurred per family was $182 for the home group and $593 for the hospital group (p<0·0001). QALYs were 0·005 for the home group versus 0·004 for the hospital group (p<0·0001).	Reported	Reported	9

APPENDIX 9: QUALITY ASSESSMENT OF ECONOMIC STUDIES USING DRUMMOND'S CHECKLIST(74)

Parameter	Hendricks et al. 2011	Teuffel et al. 2011	Teuffel et al. 2011	Theocharis et al. 2012	Al Ansari et al. 2013	Rodriguez t al. 2013	Lacroix et al. 2014	Malone et al. 2015	Ruh et al. 2015	Chrysochoou et al 2016	Kameshwar et al. 2016	Connors et al. 2017	Gonzalez et al. 2017	Hensey et al. 2017	Ibrahim et al. 2017	Pajaron et al. 2017	Burkett et al. 2018	Durojaiye et al. 2018	Psaltidikis et al. 2018	Ramasubramanian et al. 2018	Ibrahim et al. 2019
1. Well-defined of research question	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Description of adequate alternatives	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y
3. Evidence of effectiveness	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
4. Relevance of the costs and consequences	Y	Y	Y	N	N	N	Y	Y	Y	N	Y	N	Y	N	N	N	Y	Y	Y	N	Y
5. Accuracy of the costs and consequences	Y	Y	Y	N	N	N	N	N	Y	N	Y	N	Y	N	N	N	N	Y	N	N	Y
6. Credibility of the value of the costs and consequences	Y	Y	Y	N	N	N	N	N	N	N	Y	Y	Y	N	N	N	N	Y	Y	N	Y
7. Discounting used as appropriate	N	Y	Y	N	N	N	NA	N	N	NA	N	NA	N	N	NA	N	NA	N	Y	N	N

8. Incremental analyses appropriately reported	N	Y	Y	N	N	N	N	N	N	N	N	NA	NA	N	N	N	N	N	Y	N	Y
9. Sensitivity analyses reported	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	Y
10. Adequate discussion	Y	Y	Y	N	N	N	N	N	Y	N	Y	Y	Y	N	N	Y	N	Y	Y	Y	Y
No. of items met	8	10	10	2	3	2	4	3	6	4	6	6	7	3	4	4	5	7	9	2	9

N: no; Y: yes; NA: not applicable.

APPENDIX 10: ACTIVITIES AND OTHER RESOURCE USE APPLIED IN THE MICRO-COSTING ANALYSES

Activity	Estimate	Unit	Source
IV treatment in the hospital (hospital nurse time)	30 min	per IV treatment	Clinical experts
IV treatment in the infusion/health centre (community nurse time)	30 min	per IV treatment	Clinical experts
IV treatment in the patient's home (community nurse time)	45 min, except first visit 1 hour	per IV treatment	Inspired by Minton et al. (2017), adjusted in cooperation with clinical experts
IV treatment in the patient's home (community nurse time + pump)	25 min, except first visit 45 min	per IV treatment	Inspired by Minton et al. (2017), adjusted in cooperation with clinical experts
Clinical evaluation (hospital)	15 min nurse time, 15 min physician time	per evaluation	Assumptions: inpatient = one daily clinical evaluation, OPAT = one clinical evaluation, and for OPAT treatment >7 days = one clinical evaluation per 7 treatment days. Clinical experts
Change of MID-line/Picc-line	30 min nurse time, 30 min physician time	per change	Assume one change per patient when number of treatment days >7. Clinical experts
Medicines pick-up (hospital)	15 min nurse time	per pick-up	Clinical experts
IV treatment start-up (hospital)	15 min nurse time	per day	Clinical experts
Administration (paperwork/communication) (community and hospital nurse)	10 min nurse time	per day	Clinical experts
Training session (duplex, electronic or elastomeric pump)	3 hours nurse time	per episode	Assumed resource use includes information, shared decision making, and training (infusion + tele-monitoring). Clinical experts
Telephone or email consultation	DRG-tariff		Assume 2 consultations per 7 days
Travel distance t/r hospital	28 km		Medicinrådet (2020)
Travel distance t/r community office to patient	28 km		Own estimate based on average travel distance t/r hospital
Travel distance t/r infusion/health centre	14 km		Own estimate based on half the average travel distance t/r hospital
Waiting time (hospital outpatient clinic or infusion/health centre)	13 min	per visit	Jørgensen, A. and J. Toft (2017)
Number of treatment days after hospitalisation (spondylodiscitis)	21 days		Clinical experts
Number of treatment days after hospitalisation (febrile neutropenia)	5 days		Clinical experts
Number of treatment days after hospitalisation (pneumonia)	3 days		Akutteam Odense (2020)
Number of treatment days after acute contact, no hospitalisation (pneumonia)	15 days		Assumption based on trim point for the diagnosis in the Danish DRG-system, Sundhedsstyrelsen (2020)
Number of IV treatments per day	1-3 infusions		Number of infusions dependent on prescribed medication and possible delivery forms. Hospital pharmacy, and clinical experts

APPENDIX 11: UNIT COSTS APPLIED IN THE ANALYSES

Activity	Unit	Cost per unit (2020-€)	Source
Hospital admission (pneumonia, patient age > 60)	per admission	4816,50	Danish DRG-tariff: 04MA13. Sundhedsstyrelsen (2020)
Bed day in the hospital	per day	276,51	Danish bed day tariff. Sundhedsstyrelsen (2020)
Telephone or email consultation	per event	16,77	Danish DRG-tariff: 65TE01. Sundhedsstyrelsen (2020)
Value of patient time	per hour	23,27	Medicinrådet (2020)
Value of hospital nurse time	per hour	72,02	Medicinrådet (2020)
Value of community nurse time (infusion-/health centre)	per hour	71,50	Medicinrådet (2020)
Value of community nurse time (treatment at home)	per hour	89,38	Recommended hourly cost X 1.25
Value of physician time	per hour	171,08	Medicinrådet (2020)
Travel cost	per km	0,46	National reimbursement rate. Medicinrådet (2020)
Travel time costs for patients t/r hospital	per event	13,00	Medicinrådet (2020)
Travel time costs for patients t/r infusion-/health centre	per event	6,50	Half the travel cost t/r hospital
Tele-monitoring - start-up costs	per patient	31,85	Based on TeleCare Nord data, adjusted for this analysis by Flemming Witt Udsen[1]
Tele-monitoring - running costs	per day	1,47	
Electronic pump (CADD-Solis)	per day	19,08	Own calculations[2]
Medication			
Piperacillin/Tazobactam 4mg + 0,5g (3 doses per day)	per day	16,37	Cost per day includes 3 doses, natriumclorid and infusion sets. Hospital Pharmacy, Central Denmark Region
Piperacillin/Tazobactam 9mg/ml 12g/1,5g - Ready-to-use infusion bag	per day	52,28	Cost per day includes one infusion bag, and infusion set. Hospital Pharmacy, Central Denmark Region
Elastomeric pump (Folfusor) Piperacillin/Tazobactam 9mg/ml 12g/1,5g	per day	97,67	Hospital Pharmacy, Central Denmark Region
Cefuroxime 750mg (3 doses per day)	per day	8,75	Cost per day includes 3 doses, natriumclorid and infusion set. Hospital Pharmacy of Funen
Cefuroxime 750mg - Duplex (3 doses per day)	per day	28,95	Cost per day includes 3 doses and infusion sets. Hospital Pharmacy of Funen
Ceftriaxone 2g (1 dose per day)	per day	3,50	Cost per day includes 1 dose, natriumclorid and infusion set. Hospital Pharmacy of Funen
Ceftriaxone 2g - Divibax (1 dose per day)	per day	9,84	Cost per day includes 1 dose and infusion set. Hospital Pharmacy, Central Denmark Region
Elastomeric pump (EasyPump) Ceftriaxone 2g	per day	77,09	Hospital Pharmacy of Funen

[1]Tele-monitoring start-up costs included cleaning, disposable leaflet, and CRP-kit for each patient. Tele-monitoring running costs were calculated as follows: Cost of tablet and monitoring devices (tele-kit) 1300 € was calculated as an equivalent annual cost, using an estimated life time of 5 years and an interest rate of 0%. Annual licence, service costs and IT-running costs were calculated based on TeleCare Nord data assuming a volume of 10.000 tele-kits. Total running costs were calculated as a daily cost assuming 150 days of use per year.
[2]Daily cost of the electronic pump (CADD Solis) were calculated as follows: Cost of the electronic pump 2600 € and carriers bag 78 € was calculated as an equivalent annual cost, using an estimated life time of 5 years and an interest rate of 0%. Annual costs of service, cleaning and nurse education were added the equivalent annual cost. The annual costs were calculated as daily operating cost assuming 150 days of use per year. Daily cost of batteries and infusion set were added to the daily operating cost to get the total daily cost of the electronic pump.

APPENDIX 12: MICRO-COSTING ANALYSES OF RELEVANT CARE MODELS WITHIN EACH DIAGNOSTIC CASE

Diagnostic case: Spondylodiscitis

Treatment days at home	21
Number of IV administrations per day (Ceftriaxone 2g)	1

Resource use	Mean cost (2020-€)	Source
Inpatient		
Inpatient stay per day	5807	Long term bed cost
IV treatment	756	Assume that a hospital nurse spends 30 min per IV treatment.
Clinical evaluation (daily)	1276	Assume 15 min nurse time and 15 min physician time per treatment day.
Medication costs	74	Ceftriaxone 2g.
Total	**7913**	
Outpatient treatment (hospital)		
Model 1 (daily infusion in the outpatient clinic)		
IV treatment	756	Assume that a hospital nurse spends 30 min per IV treatment.
Clinical evaluation	182	Evaluation once a week during IV treatment. Assume 15 min nurse time and 15 min physician time per treatment day.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time
Medication costs	74	Ceftriaxone 2g.
Patient-borne costs (travel each day)		
Travel costs	269	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	273	Travel time cost for patients multiplied with the number of visits
Waiting time costs	106	Assume mean waiting time of 13 min in the outpatient clinic
Total	**1782**	
Model 2 (electronic pump + daily visit in the outpatient clinic)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Daily visits (IV treatment start-up)	751	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Clinical evaluation	182	Evaluation once a week during IV treatment. Assume 15 min nurse time and 15 min physician time per treatment day.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time

Cost electronic pump (CADD)	401	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	74	Ceftriaxone 2g.
Patient-borne costs (travel each day)		
Travel costs	269	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	273	Travel time cost for patients multiplied with the number of visits
Waiting time costs	106	Assume mean waiting time of 13 min in the outpatient clinic
Total	**2393**	
Model 3 (elastomeric pump + daily visit in the outpatient clinic)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Daily visits (IV treatment start-up)	751	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Clinical evaluation	182	Evaluation once a week during IV treatment. Assume 15 min nurse time and 15 min physician time per treatment day.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time
Medication costs	1619	Ceftriaxone 2g (EasyPump)
Patient-borne costs (travel each day)		
Travel costs	269	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	273	Travel time cost for patients multiplied with the number of visits
Waiting time costs	106	Assume mean waiting time of 13 min in the outpatient clinic
Total	**3538**	
Outpatient treatment (infusion-/health centre)		
Model 1 (daily infusions in the infusion/health centre)		
Outpatient IV treatment in infusion-/health centre	751	Assume that a community nurse spends 30 min per IV treatment.
Administration (paperwork/communication) (community nurse)	255	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	257	Assume 10 minutes per treatment day.
Hospital visits (clinical evaluation/medicine pick up)	236	Visit once a week during IV treatment. Assume 15 min nurse time for medicine preparation, 15 min nurse time per clinical evaluation, and 15 min physician time spend per clinical evaluation.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time
Medication costs	74	Ceftriaxone 2g.

Patient-borne costs (travel each day)		
Travel costs	173	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of visits . Travel cost per hospital visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of visits
Travel time costs	137	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits. Travel time costs t/r hospital multiplied with number of visits.
Waiting time costs	121	Assume mean waiting time of 13 min
Total	**2125**	
Model 2 (electronic pump + daily visit in the infusion/health centre)		
Not applicable - medication not available in infusion bag for electronic pump		
Model 3 (elastomeric pump + daily visit in the infusion/health centre)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Daily visits (IV treatment start-up)	751	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Administration (paperwork/communication) (community nurse)	255	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	257	Assume 10 minutes per treatment day.
Hospital visits (clinical evaluation/medicine pick up)	236	Visit once a week during IV treatment. Assume 15 min nurse time for medicine preparation, 15 min nurse time per clinical evaluation, and 15 min physician time spend per clinical evaluation.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time
Medication costs	1619	Ceftriaxone 2g (EasyPump)
Patient-borne costs (travel each day)		
Travel costs	173	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of visits . Travel cost per hospital visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of visits
Travel time costs	137	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits. Travel time costs t/r hospital multiplied with number of visits.
Waiting time costs	121	Assume mean waiting time of 13 min
Total	**3886**	
Home-IV (community nurse)		
Model 1 (community nurse visit for each infusion)		
Community nurse visits	1430	Community nurse. Each visit = 45 min except first, which = 1 hour.
Administration (paperwork/communication) (community nurse)	319	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	257	Assume 10 minutes per treatment day.

Hospital visits (clinical evaluation/medicine pick up)	236	Visit once a week during IV treatment. Assume 15 min nurse time for medicine preparation, 15 min nurse time per clinical evaluation, and 15 min physician time spend per clinical evaluation.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time
Medication costs	74	Ceftriaxone 2g.
Patient-borne costs (travel once a week)		
Travel costs	38	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	39	Travel time cost for patients multiplied with the number of visits
Waiting time costs	15	Assume mean waiting time of 13 min in the outpatient clinic
Total	**2530**	
Model 2 (electronic pump + community nurse)		
Not applicable - medication not available in infusion bag for electronic pump		
Model 3 (elastomeric pump + community nurse)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Community nurse visit (one daily visit)	752	Community nurse. Each visit = 25 min except first, which = 45 min.
Administration (paperwork/communication) (community nurse)	319	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	257	Assume 10 minutes per treatment day.
Hospital visits (clinical evaluation/medicine pick up)	236	Visit once a week during IV treatment. Assume 15 min nurse time for medicine preparation, 15 min nurse time per clinical evaluation, and 15 min physician time spend per clinical evaluation.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time
Medication costs	1619	Ceftriaxone 2g. (EasyPump)
Patient-borne costs (travel once a week)		
Travel costs	38	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	39	Travel time cost for patients multiplied with the number of visits
Waiting time costs	15	Assume mean waiting time of 13 min in the outpatient clinic
Total	**3613**	
Home-IV (self-administration)		
Model 1 (electronic pump + tele-monitoring)		
Not applicable - medication not available in infusion bag for electronic pump		
Model 2 (elastomeric pump + tele-monitoring)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.

Administration (paperwork/communication) (hospital nurse)	257	Assume 10 minutes per treatment day.
Telephone or email consultation	101	Danish DRG-tariff: 65TE01, Assume 2 contacts per week.
Hospital visits (clinical evaluation/medicine pick up)	236	Visit once a week during IV treatment. Assume 15 min nurse time for medicine preparation, 15 min nurse time per clinical evaluation, and 15 min physician time spend per clinical evaluation.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time
Start-up cost tele-monitoring	32	Per patient cost
Running costs tele-monitoring	31	Daily tele-monitoring cost multiplied by number of treatment days
Medication costs	1619	Ceftriaxone 2g (EasyPump)
Patient-borne costs (travel once a week)		
Travel costs	38	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	39	Travel time cost for patients multiplied with the number of visits
Waiting time costs	15	Assume mean waiting time of 13 min in the outpatient clinic
Total	**2706**	
Model 3 (Duplex/Divibax + tele-monitoring)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Administration (paperwork/communication) (hospital nurse)	257	Assume 10 minutes per treatment day.
Telephone or email consultation	101	Danish DRG-tariff: 65TE01, Assume 2 contacts per week.
Hospital visits (clinical evaluation/medicine pick up)	236	Visit once a week during IV treatment. Assume 15 min nurse time for medicine preparation, 15 min nurse time per clinical evaluation, and 15 min physician time spend per clinical evaluation.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time
Start-up cost tele-monitoring	32	Per patient cost
Running costs tele-monitoring	31	Daily tele-monitoring cost multiplied by number of treatment days
Medication costs	207	Ceftriaxone 2g (Divibax)
Patient-borne costs (travel once a week)		
Travel costs	38	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	39	Travel time cost for patients multiplied with the number of visits
Waiting time costs	15	Assume mean waiting time of 13 min in the outpatient clinic
Total	**1294**	

Diagnostic case: Spondylodiscitis

Treatment days at home	21
Number of IV administrations per day (Cefuroxime 750 mg)	3

Resource use	Mean cost (2020-€)	Source
Inpatient		
Inpatient stay per day	5807	Long term bed cost
IV treatment	2269	Assume that a hospital nurse spends 30 min per IV treatment.
Clinical evaluation (daily)	1276	Assume 15 min nurse time and 15 min physician time per treatment day.
Medication costs	184	Cefuroxime 750mg.
Total	**9535**	
Outpatient treatment (hospital)		
Model 1 (daily infusion in the outpatient clinic)		
Not applicable - number of daily infusions makes the model clinically irrelevant		
Model 2 (electronic pump + daily visit in the outpatient clinic)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
IV treatment	756	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Clinical evaluation	182	Evaluation once a week during IV treatment. Assume 15 min nurse time and 15 min physician time per treatment day.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time
Cost electronic pump (CADD)	401	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	184	Cefuroxime 750mg.
Patient-borne costs (travel each day)		
Travel costs	269	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	273	Travel time cost for patients multiplied with the number of visits
Waiting time costs	106	Assume mean waiting time of 13 min in the outpatient clinic
Total	**2509**	
Model 3 (elastomeric pump + daily visit in the outpatient clinic)		

Not applicable - medication not available in elastomeric pump		
Outpatient treatment (infusion-/health centre)		
Model 1 (daily infusions in the infusion/health centre)		
Outpatient IV treatment in infusion-/health centre	2252	Assume that a community nurse spends 30 min per IV treatment.
Administration (paperwork/communication) (community nurse)	255	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	257	Assume 10 minutes per treatment day.
Hospital visits (clinical evaluation/medicine pick up)	236	Visit once a week during IV treatment. Assume 15 min nurse time for medicine preparation, 15 min nurse time per clinical evaluation, and 15 min physician time spend per clinical evaluation.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time
Medication costs	184	Cefuroxime 750mg.
Patient-borne costs (travel for each infusion)		
Travel costs	442	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day. Travel cost per hospital visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of visits
Travel time costs	449	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits. Travel time costs t/r hospital multiplied with number of visits.
Waiting time costs	333	Assume mean waiting time of 13 min in the outpatient clinic
Total	**4530**	
Model 2 (electronic pump + daily visit in the infusion/health centre)		
Not applicable - medication not available in infusion bag for electronic pump		
Model 3 (elastomeric pump + daily visit in the infusion/health centre)		
Not applicable - medication not available in elastomeric pump		
Home-IV (community nurse)		
Model 1 (community nurse visit for each infusion)		
Community nurse visits	4245	Community nurse. Each visit = 45 min except first, which = 1 hour.
Administration (paperwork/communication) (community nurse)	319	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	257	Assume 10 minutes per treatment day.
Hospital visits (clinical evaluation/medicine pick up)	236	Visit once a week during IV treatment. Assume 15 min nurse time for medicine preparation, 15 min nurse time per clinical evaluation, and 15 min physician time spend per clinical evaluation.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time
Medication costs	184	Cefuroxime 750mg.

Patient-borne costs (travel once a week)		
Travel costs	38	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	39	Travel time cost for patients multiplied with the number of visits
Waiting time costs	15	Assume mean waiting time of 13 min in the outpatient clinic
Total	**5456**	
Model 2 (electronic pump + community nurse)		
Not applicable - medication not available in infusion bag for electronic pump		
Model 3 (elastomeric pump + community nurse)		
Not applicable - medication not available in elastomeric pump		
Home-IV (self-administration)		
Model 1 (electronic pump + tele-monitoring)		
Not applicable - medication not available in infusion bag for electronic pump		
Model 2 (elastomeric pump + tele-monitoring)		
Not applicable - medication not available in elastomeric pump		
Model 3 (Duplex/Divibax + tele-monitoring)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Administration (paperwork/communication) (hospital nurse)	257	Assume 10 minutes per treatment day.
Telephone or email consultation	101	Danish DRG-tariff: 65TE01, Assume 2 contacts per week.
Hospital visits (clinical evaluation/medicine pick up)	236	Visit once a week during IV treatment. Assume 15 min nurse time for medicine preparation, 15 min nurse time per clinical evaluation, and 15 min physician time spend per clinical evaluation.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time
Start-up cost tele-monitoring	32	Per patient cost
Running costs tele-monitoring	31	Daily tele-monitoring cost multiplied by number of treatment days
Medication costs	620	Cefuroxime 750mg (Divibax)
Patient-borne costs (travel once a week)		
Travel costs	38	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	39	Travel time cost for patients multiplied with the number of visits
Waiting time costs	15	Assume mean waiting time of 13 min in the outpatient clinic
Total	**1707**	

Diagnostic case: Febrile Neutropenia

Treatment days at home	5
Number of IV administrations per day (Ususal medication)	3
Number of IV administrations per day (Ready-To-Use medication)	1

Resource use	Mean cost (2020-€)	Source
Inpatient		
Inpatient stay per day	1383	Long term bed cost
IV treatment	540	Assume that a hospital nurse spends 30 min per IV treatment.
Clinical evaluation (daily)	304	Assume 15 min nurse time and 15 min physician time per treatment day.
Medication costs	82	Piperacillin/Tazobactam 4mg + 0,5g
Total	**2308**	
Outpatient treatment (hospital)		
Model 1 (daily infusion in the outpatient clinic)		
Not applicable - number of daily infusions makes the model clinically irrelevant		
Model 2 (electronic pump + daily visit in the outpatient clinic)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
IV treatment	180	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Cost electronic pump (CADD)	95	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	82	Piperacillin/Tazobactam 4mg + 0,5g
Patient-borne costs (travel each day)		
Travel costs	64	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	65	Travel time cost for patients multiplied with the number of visits
Waiting time costs	25	Assume mean waiting time of 13 min in the outpatient clinic
Total	**728**	
Model 3 (elastomeric pump + daily visit in the outpatient clinic)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.

IV treatment	180	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Medication costs	488	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Elastomeric pump - Fulfusor)
Patient-borne costs (travel each day)		
Travel costs	64	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	65	Travel time cost for patients multiplied with the number of visits
Waiting time costs	25	Assume mean waiting time of 13 min in the outpatient clinic
Total	**1039**	
Outpatient treatment (infusion-/health centre)		
Model 1 (daily infusions in the infusion/health centre)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Outpatient IV treatment in a community infusion-/health centre	536	Assume that a community nurse spends 30 min per IV treatment.
Administration (paperwork/communication) (community nurse)	61	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	61	Assume 10 minutes per treatment day.
Medication costs	82	Piperacillin/Tazobactam 4mg + 0,5g
Patient-borne costs (travel for each infusion)		
Travel costs	122	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day. Travel cost per hospital visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of visits
Travel time costs	124	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits. Travel time costs t/r hospital multiplied with number of visits.
Waiting time costs	86	Assume mean waiting time of 13 min in the outpatient clinic
Total	**1287**	
Model 2 (electronic pump + daily visit in the infusion/health centre)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Outpatient IV treatment in a infusion-/health centre	536	Assume that a community nurse spends 30 min per IV treatment.
Administration (paperwork/communication) (community nurse)	61	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	61	Assume 10 minutes per treatment day.
Cost electronic pump (CADD)	95	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	261	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Ready-to-use infusion bag)

Patient-borne costs (travel each day)		
Travel costs	58	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day. Travel cost per hospital visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of visits
Travel time costs	59	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits. Travel time costs t/r hospital multiplied with number of visits.
Waiting time costs	35	Assume mean waiting time of 13 min in the outpatient clinic
Total	**1383**	
Model 3 (elastomeric pump + daily visit in the infusion/health centre)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Outpatient IV treatment in a infusion-/health centre	536	Assume that a community nurse spends 30 min per IV treatment.
Administration (paperwork/communication) (community nurse)	61	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	61	Assume 10 minutes per treatment day.
Medication costs	488	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Elastomeric pump - Fulfusor)
Patient-borne costs (travel each day)		
Travel costs	58	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day. Travel cost per hospital visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of visits
Travel time costs	59	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits. Travel time costs t/r hospital multiplied with number of visits.
Waiting time costs	35	Assume mean waiting time of 13 min in the outpatient clinic
Total	**1514**	
Home-IV (community nurse)		
Model 1 (community nurse visit for each infusion)		
Community nurse visits	1028	Community nurse. Each visit = 45 min except first, which = 1 hour.
Administration (paperwork/communication) (district nurse)	76	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	61	Assume 10 minutes per treatment day.
Medication costs	82	Piperacillin/Tazobactam 4mg + 0,5g
Total	**1247**	
Model 2 (electronic pump + community nurse)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Community nurse visit (one daily visit)	151	Community nurse. Each visit = 25 min except first, which = 45 min.

Administration (paperwork/communication) (community nurse)	76	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	61	Assume 10 minutes per treatment day.
Cost electronic pump (CADD)	95	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	261	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Ready-to-use infusion bag)
Total	**861**	
Model 3 (elastomeric pump + community nurse)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Community nurse visit (one daily visit)	151	Community nurse. Each visit = 25 min except first, which = 45 min.
Administration (paperwork/communication) (community nurse)	76	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	61	Assume 10 minutes per treatment day.
Medication costs	488	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Elastomeric pump - Fulfusor)
Total	**992**	
Home-IV (self-administration)		
Model 1 (electronic pump + tele-monitoring)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Administration (paperwork/communication) (hospital nurse)	61	Assume 10 minutes per treatment day.
Telephone or email consultation	61	Danish DRG-tariff: 65TE01, Assume 1 contact.
Start-up cost telemonitoring	32	Per patient cost
Running costs telemonitoring	7	Daily telemonitoring cost multiplied by number of treatment days
Cost electronic pump (CADD)	95	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	157	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Ready-to-use infusion bag)
Total	**629**	
Model 2 (elastomeric pump + tele-monitoring)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Administration (paperwork/communication) (hospital nurse)	61	Assume 10 minutes per treatment day.
Telephone or email consultation	17	Danish DRG-tariff: 65TE01, Assume 1 contact.
Start-up cost tele-monitoring	32	Per patient cost
Running costs tele-monitoring	7	Daily tele-monitoring cost multiplied by number of treatment days
Medication costs	488	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Elastomeric pump - Fulfusor)
Total	**822**	
Model 3 (Duplex/Divibax + tele-monitoring)		
Not applicable		

Diagnostic case: Pneumonia

Treatment days at home	3
Number of IV administrations per day (Ususal medication)	3
Number of IV administrations per day (Ready-To-Use medication)	1

Resource use	Mean cost (2020-€)	Source
Inpatient		
Inpatient stay per day	830	Long term bed cost
IV treatment	1052	Assume that a hospital nurse spends 30 min per IV treatment
Clinical evaluation (daily)	182	Assume 15 min nurse time and 15 min physician time per treatment day
Medication costs	49	Piperacillin/Tazobactam 4mg + 0,5g
Total	**2113**	
Outpatient treatment (hospital)		
Model 1 (daily infusion in the outpatient clinic)		
Not applicable - number of daily infusions makes the model clinically irrelevant		
Model 2 (electronic pump + daily visit in the outpatient clinic)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Daily visits (IV treatment start-up)	108	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Cost electronic pump (CADD)	57	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	49	Piperacillin/Tazobactam 4mg + 0,5g
Patient-borne costs (travel each day)		
Travel costs	38	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	39	Travel time cost for patients multiplied with the number of visits
Waiting time costs	15	Assume mean waiting time of 13 min in the outpatient clinic
Total	**523**	
Model 3 (elastomeric pump + daily visit in the outpatient clinic)		

Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Daily visits (IV treatment start-up)	108	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Medication costs	293	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Elastomeric pump - Fulfusor)
Patient-borne costs (travel each day)		
Travel costs	19	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	20	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits
Waiting time costs	15	Assume mean waiting time of 13 min in the outpatient clinic
Total	**671**	
Outpatient treatment (infusion-/health centre)		
Model 1 (daily infusions in the infusion/health centre)		
Outpatient IV treatment in a infusion-/health centre	322	Assume that a community nurse spends 30 min per IV treatment.
Administration (paperwork/communication) (community nurse)	36	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	37	Assume 10 minutes per treatment day.
Medication costs	49	Piperacillin/Tazobactam 4mg + 0,5g
Patient-borne costs (travel for each infusion)		
Travel costs	58	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	59	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits
Waiting time costs	45	Assume mean waiting time of 13 min in the outpatient clinic
Total	**606**	
Model 2 (electronic pump + daily visit in the infusion/health centre)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Daily visits (IV treatment start-up)	107	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Administration (paperwork/communication) (community nurse)	36	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	37	Assume 10 minutes per treatment day.

Cost electronic pump (CADD)	57	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	157	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Ready-to-use infusion bag)
Patient-borne costs (travel each day)		
Travel costs	19	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	20	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits
Waiting time costs	15	Assume mean waiting time of 13 min in the outpatient clinic
Total	**664**	
Model 3 (elastomeric pump + daily visit in the infusion/health centre)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Daily visits (IV treatment start-up)	107	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Administration (paperwork/communication) (community nurse)	36	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	37	Assume 10 minutes per treatment day.
Medication costs	293	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Elastomeric pump - Fulfusor)
Patient-borne costs (travel each day)		
Travel costs	19	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	20	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits
Waiting time costs	15	Assume mean waiting time of 13 min in the outpatient clinic
Total	**743**	
Home-IV (community nurse)		
Model 1 (community nurse visit for each infusion)		
Community nurse visits	626	Community nurse. Each visit = 45 min except first, which = 1 hour.
Administration (paperwork/communication) (district nurse)	46	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	37	Assume 10 minutes per treatment day.
Medication costs	49	Piperacillin/Tazobactam 4mg + 0,5g
Total	**757**	
Model 2 (electronic pump + community nurse)		

Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Community nurse visit (one daily visit)	76	Community nurse. Each visit = 25 min except first, which = 45 min.
Administration (paperwork/communication) (community nurse)	46	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	37	Assume 10 minutes per treatment day.
Cost electronic pump (CADD)	57	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	157	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Ready-to-use infusion bag)
Total	**588**	
Model 3 (elastomeric pump + community nurse)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Community nurse visit (one daily visit)	76	Community nurse. Each visit = 25 min except first, which = 45 min.
Administration (paperwork/communication) (community nurse)	46	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	37	Assume 10 minutes per treatment day.
Medication costs	293	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Elastomeric pump - Fulfusor)
Total	**667**	
Home-IV (self-administration)		
Model 1 (electronic pump + tele-monitoring)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Administration (paperwork/communication) (hospital nurse)	37	Assume 10 minutes per treatment day.
Telephone or email consultation	17	Danish DRG-tariff: 65TE01, Assume 1 contact.
Start-up cost tele-monitoring	32	Per patient cost
Running costs tele-monitoring	4	Daily tele-monitoring cost multiplied by number of treatment days
Cost electronic pump (CADD)	57	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	157	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Ready-to-use infusion bag)
Total	**520**	
Model 2 (elastomeric pump + tele-monitoring)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Administration (paperwork/communication) (hospital nurse)	37	Assume 10 minutes per treatment day.
Telephone or email consultation	17	Danish DRG-tariff: 65TE01, Assume 1 contact.
Start-up cost tele-monitoring	32	Per patient cost
Running costs tele-monitoring	4	Daily tele-monitoring cost multiplied by number of treatment days

Medication costs	293	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Elastomeric pump - Fulfusor)
Total	**599**	
Model 3 (Duplex/Divibax)		
Not applicable		

Diagnostic case: Acute Pneumonia

Treatment days at home - hospital admission avoided	15
Number of IV administrations per day (Ususal medication)	3
Number of IV administrations per day (Ready-To-Use medication)	1

Resource use	Mean cost (2020-€)	Source
Inpatient		
Inpatient stay	4817	Danish DRG-tariff: 04MA13
Total	**4817**	
Outpatient treatment (hospital)		
Model 1 (daily infusion in the outpatient clinic)		
Not applicable - number of daily infusions makes the model clinically irrelevant		
Model 2 (electronic pump + daily visit in the outpatient clinic)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
IV treatment	540	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Clinical evaluation	122	Evaluation once a week during IV treatment. Assume 15 min nurse and 15 min physician time.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time. Assume one change
Cost electronic pump (CADD)	286	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	246	Piperacillin/Tazobactam 4mg + 0,5g
Patient-borne costs (travel each day)		

Travel costs	192	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	195	Travel time cost for patients multiplied with the number of visits
Waiting time costs	76	Assume mean waiting time of 13 min in the outpatient clinic
Total	**1994**	
Model 3 (elastomeric pump + daily visit in the outpatient clinic)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
IV treatment	540	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Clinical evaluation	122	Evaluation once a week during IV treatment. Assume 15 min nurse and 15 min physician time.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time. Assume one change
Medication costs	1465	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Elastomeric pump - Fulfusor)
Patient-borne costs (travel each day)		
Travel costs	96	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	98	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits
Waiting time costs	76	Assume mean waiting time of 13 min in the outpatient clinic
Total	**2734**	
Outpatient treatment (infusion-/health centre)		
Model 1 (daily infusions in the infusion/health centre)		
Outpatient IV treatment in a community infusion-/health centre	1609	Assume that a community nurse spends 30 min per IV treatment.
Administration (paperwork/communication) (community nurse)	182	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	184	Assume 10 minutes per treatment day.
Hospital visit (clinical evaluation)	122	Evaluation once a week during IV treatment. Assume 15 min nurse and 15 min physician time.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time. Assume one change
Medication costs	246	Piperacillin/Tazobactam 4mg + 0,5g
Patient-borne costs (travel for each infusion)		
Travel costs	314	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day. Travel cost per hospital visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of visits

Travel time costs	319	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits. Travel time costs t/r hospital multiplied with number of visits.
Waiting time costs	237	Assume mean waiting time of 13 min in the outpatient clinic
Total	**3333**	
Model 2 (electronic pump + daily visit in the infusion/health centre)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Daily visits (IV treatment start-up)	536	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Administration (paperwork/communication) (community nurse)	182	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	184	Assume 10 minutes per treatment day.
Hospital visit (clinical evaluation)	122	Evaluation once a week during IV treatment. Assume 15 min nurse and 15 min physician time.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time. Assume one change
Cost electronic pump (CADD)	286	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	784	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Ready-to-use infusion bag)
Patient-borne costs (travel each day)		
Travel costs	122	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day. Travel cost per hospital visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of visits
Travel time costs	124	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits. Travel time costs t/r hospital multiplied with number of visits.
Waiting time costs	86	Assume mean waiting time of 13 min in the outpatient clinic
Total	**2763**	
Model 3 (elastomeric pump + daily visit in the infusion/health centre)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Daily visits (IV treatment start-up)	536	Daily visit for start-up of IV treatment. Assume 15 min nurse time for medicine preparation and 15 min IV treatment start.
Administration (paperwork/communication) (community nurse)	182	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	184	Assume 10 minutes per treatment day.
Hospital visit (clinical evaluation)	122	Evaluation once a week during IV treatment. Assume 15 min nurse and 15 min physician time.

Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time. Assume one change
Medication costs	1465	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Elastomeric pump - Fulfusor)
Patient-borne costs (travel each day)		
Travel costs	122	Travel cost per visit (14 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day. Travel cost per hospital visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of visits
Travel time costs	124	Travel time cost for patients t/r infusion-/health centre multiplied with the number of visits. Travel time costs t/r hospital multiplied with number of visits.
Waiting time costs	86	Assume mean waiting time of 13 min in the outpatient clinic
Total	**3157**	
Home-IV (community nurse)		
Model 1 (community nurse visit for each infusion)		
Community nurse visits	3039	Community nurse. Each visit = 45 min except first, which = 1 hour.
Administration (paperwork/communication) (district nurse)	228	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	184	Assume 10 minutes per treatment day.
Hospital visit (clinical evaluation)	122	Evaluation once a week during IV treatment. Assume 15 min nurse and 15 min physician time.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time. Assume one change
Medication costs	737	Piperacillin/Tazobactam 4mg + 0,5g
Patient-borne costs (travel twice during episode)		
Travel costs	26	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	26	Travel time cost for patients multiplied with the number of visits
Waiting time costs	10	Assume mean waiting time of 13 min in the outpatient clinic
Total	**4492**	
Model 2 (electronic pump + community nurse)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Community nurse visit (one daily visit)	526	Community nurse. Each visit = 25 min except first, which = 45 min.
Administration (paperwork/communication) (community nurse)	228	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	184	Assume 10 minutes per treatment day.
Hospital visit (clinical evaluation)	122	Evaluation once a week during IV treatment. Assume 15 min nurse and 15 min physician time.

Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time. Assume one change
Cost electronic pump (CADD)	286	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	784	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Ready-to-use infusion bag)
Patient-borne costs (travel twice during episode)		
Travel costs	26	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	26	Travel time cost for patients multiplied with the number of visits
Waiting time costs	10	Assume mean waiting time of 13 min in the outpatient clinic
Total	**2529**	
Model 3 (elastomeric pump + community nurse)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Community nurse visit (one daily visit)	526	Community nurse. Each visit = 25 min except first, which = 45 min.
Administration (paperwork/communication) (community nurse)	228	Assume 10 minutes per treatment day.
Administration (paperwork/communication) (hospital nurse)	184	Assume 10 minutes per treatment day.
Hospital visit (clinical evaluation)	122	Evaluation once a week during IV treatment. Assume 15 min nurse and 15 min physician time.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time. Assume one change
Medication costs	1465	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Elastomeric pump - Fulfusor)
Patient-borne costs (travel twice during episode)		
Travel costs	26	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	26	Travel time cost for patients multiplied with the number of visits
Waiting time costs	10	Assume mean waiting time of 13 min in the outpatient clinic
Total	**2924**	
Home-IV (self-administration)		
Model 1 (electronic pump + tele-monitoring)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Administration (paperwork/communication) (hospital nurse)	184	Assume 10 minutes per treatment day.
Telephone or email consultation	72	Danish DRG-tariff: 65TE01, Assume 2 contacts per week.
Hospital visit (clinical evaluation)	122	Evaluation once a week during IV treatment. Assume 15 min nurse and 15 min physician time.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time. Assume one change

Start-up cost tele-monitoring	32	Per patient cost
Running costs tele-monitoring	22	Daily tele-monitoring cost multiplied by number of treatment days
Cost electronic pump (CADD)	286	Assume 10 years lifetime of electronic pump and 150 days annual use. Costs include; pump, carrier bag, batteries, utenciles, cleaning, service and annual nurse education.
Medication costs	784	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Ready-to-use infusion bag)
Patient-borne costs (travel twice during episode)		
Travel costs	26	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	26	Travel time cost for patients multiplied with the number of visits
Waiting time costs	10	Assume mean waiting time of 13 min in the outpatient clinic
Total	**1901**	
Model 2 (elastomeric pump + tele-monitoring)		
Training session costs	216	Assume delivered by hospital nurse. Hourly cost X 3 hours.
Administration (paperwork/communication) (hospital nurse)	184	Assume 10 minutes per treatment day.
Telephone or email consultation	72	Danish DRG-tariff: 65TE01, Assume 2 contacts per week.
Hospital visit (clinical evaluation)	122	Evaluation once a week during IV treatment. Assume 15 min nurse and 15 min physician time.
Change of MID-line/PICC-line	122	Assume 30 min physician time, and 30 min nurse time. Assume one change
Start-up cost tele-monitoring	32	Per patient cost
Running costs tele-monitoring	22	Daily tele-monitoring cost multiplied by number of treatment days
Medication costs	1465	Piperacillin/Tazobactam 9mg/ml 12g/1,5g (Elastomeric pump - Fulfusor)
Patient-borne costs (travel twice during episode)		
Travel costs	26	Travel cost per visit (28 km x national reimbursement rate of 0.46 per km) multiplied by number of treatment days and number of visits per day
Travel time costs	26	Travel time cost for patients multiplied with the number of visits
Waiting time costs	10	Assume mean waiting time of 13 min in the outpatient clinic
Total	**2295**	
Model 3 (Duplex/Divibax + tele-monitoring)		
Not applicable		

APPENDIX 13: SENSITIVITY ANALYSIS OF COST DIFFERENCES (hourly cost community nurse as recommended by the Danish Medicines Council – no additional travel time costs)

	Treatment for 21 days after hospitalisation Case: Spondylodiscitis *Medication: Ceftriaxone*		**Treatment for 21 days after hospitalisation** Case: Spondylodiscitis *Medication: Cefuroxime*		**Treatment for 5 days after hospitalisation** Case: Febrile neutropenia *Medication: Piperacillin/Tazobactam*		**Treatment for 3 days after hospitalisation** Case: Pneumonia *Medication: Piperacillin/Tazobactam*		**Treatment for 15 days, hospitalisation avoided** Case: Acute pneumonia *Medication: Piperacillin/Tazobactam*	
	COMPARATOR: INPATIENT STAY									
Care model	*Δ Cost per episode*	*%*	*Δ Cost per episode*	*%*	*Δ Cost per episode*	*%*	*Δ Cost per episode*	*%*	*Δ Cost per episode*	*%*
Inpatient stay	7913	-	9535		2308	-	2113	-	4817	-
Outpatient treatment (hospital)										
Model 1 (daily infusions in the outpatient clinic)	-6131	-77%	Not applicable	-	Not applicable	-	Not applicable	-	Not applicable	-
Model 2 (electronic pump + daily visit in the outpatient clinic)	-5520	-70%	-7027	-74%	-1581	-68%	-1590	-75%	-2823	-59%
Model 3 (elastomeric pump + daily visit in the outpatient clinic)	-4375	-55%	Not applicable	-	-1270	-55%	-1442	-68%	-2083	-43%
Outpatient treatment (infusion/health centre)										
Model 1 (daily infusions in the infusion/health centre)	-5788	-73%	-5006	-52%	-1021	-44%	-1508	-71%	-1484	-31%
Model 2 (electronic pump + daily visit in the infusion/health centre)	Not applicable	-	Not applicable	-	-926	-40%	-1449	-69%	-2054	-43%
Model 2 (elastomeric pump + daily visit in the infusion/health centre)	-4026	-51%	Not applicable	-	-794	-34%	-1370	-65%	-1659	-34%
Home-IV (community nurse)										
Model 1 (community nurse visit for each infusion)	-5732	-72%	-4993	-52%	-1282	-56%	-1491	-71%	-978	-20%
Model 2 (electronic pump + community nurse)	Not applicable	-	Not applicable	-	-1493	-65%	-1549	-73%	-2438	-51%
Model 3 (elastomeric pump + community nurse)	-4514	-57%	Not applicable	-	-1361	-59%	-1470	-70%	-2043	-42%
Home-IV (self-administration)										
Model 1 (electronic pump + tele-monitoring)	Not applicable	-	Not applicable	-	-1679	-73%	-1593	-75%	-2916	-61%
Model 2 (elastomeric pump + tele-monitoring)	-5207	-66%	Not applicable	-	-1487	-64%	-1515	-72%	-2521	-52%
Model 3 (Duplex/Divibax + tele-monitoring)	-6619	-84%	-7828	-82%	Not applicable	-	Not applicable	-	Not applicable	-

APPENDIX 14: SENSITIVITY ANALYSIS OF COST DIFFERENCES (hourly cost community nurse multiplied with factor 1.5 to account for travel time costs)

	Treatment for 21 days after hospitalisation Case: Spondylodiscitis *Medication: Ceftriaxone*		**Treatment for 21 days after hospitalisation** Case: Spondylodiscitis *Medication: Cefuroxime*		**Treatment for 5 days after hospitalisation** Case: Febrile neutropenia *Medication: Piperacillin/Tazobactam*		**Treatment for 3 days after hospitalisation** Case: Pneumonia *Medication: Piperacillin/Tazobactam*		**Treatment for 15 days, hospitalisation avoided** Case: Acute pneumonia *Medication: Piperacillin/Tazobactam*	
	COMPARATOR: INPATIENT STAY									
Care model	*Δ Cost per episode*	*%*	*Δ Cost per episode*	*%*	*Δ Cost per episode*	*%*	*Δ Cost per episode*	*%*	*Δ Cost per episode*	*%*
Inpatient stay	7913	-	9535		2308	-	2113	-	4817	-
Outpatient treatment (hospital)										
Model 1 (daily infusions in the outpatient clinic)	-6131	-77%	Not applicable	-	Not applicable	-	Not applicable	-	Not applicable	-
Model 2 (electronic pump + daily visit in the outpatient clinic)	-5520	-70%	-7027	-74%	-1581	-68%	-1590	-75%	-2823	-59%
Model 3 (elastomeric pump + daily visit in the outpatient clinic)	-4375	-55%	Not applicable	-	-1270	-55%	-1442	-68%	-2083	-43%
Outpatient treatment (infusion/health centre)										
Model 1 (daily infusions in the infusion/health centre)	-5788	-73%	-5006	-52%	-1021	-44%	-1508	-71%	-1484	-31%
Model 2 (electronic pump + daily visit in the infusion/health centre)	Not applicable	-	Not applicable	-	-926	-40%	-1449	-69%	-2054	-43%
Model 2 (elastomeric pump + daily visit in the infusion/health centre)	-4026	-51%	Not applicable	-	-794	-34%	-1370	-65%	-1659	-34%
Home-IV (community nurse)										
Model 1 (community nurse visit for each infusion)	-5033	-64%	-3167	-33%	-841	-36%	-1222	-58%	329	7%
Model 2 (electronic pump + community nurse)	Not applicable	-	Not applicable	-	-1402	-61%	-1501	-71%	-2137	-44%
Model 3 (elastomeric pump + community nurse)	-4086	-52%	Not applicable	-	-1271	-55%	-1422	-67%	-1742	-36%
Home-IV (self-administration)										
Model 1 (electronic pump + tele-monitoring)	Not applicable	-	Not applicable	-	-1679	-73%	-1593	-75%	-2916	-61%
Model 2 (elastomeric pump + tele-monitoring)	-5207	-66%	Not applicable	-	-1487	-64%	-1515	-72%	-2521	-52%
Model 3 (Duplex/Divibax + tele-monitoring)	-6619	-84%	-7828	-82%	Not applicable	-	Not applicable	-	Not applicable	-

APPENDIX 15: LIST OF INFORMANTS WHO PROVIDED INPUT FOR THE ECONOMIC ANALYSES

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