Project No. 101045956
Biomarker and AI-supported FX06 therapy to prevent progression from mild and moderate to severe stages of COVID-19

Deliverable 7.2

Analysis of barriers for uptake

WP7 – Socio-economic impact and cost-effectiveness analyses (HTA)

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Contents

Partner short names

GUF	Johann Wolfgang Goethe Universität Frankfurt am Main
accelCH	accelopment Schweiz AG
ESAIC	European Society of Anaesthesiology and Intensive Care
Fraunhofer	Fraunhofer Institute for Translational Medicine and Pharmacology ITMP
F4	F4 Pharma GmbH
TAU	Tampereen Korkeakoulusaatio SR
UCD	University College Dublin
UMCG	Universitair Medisch Centrum Groningen
MiDA	Medical Intelligent Data Analytics GmbH
UHW	University Hospital Würzburg
UNIPG	Universita degli Studi di Perugia
KC	Lietuvos Sveikatos Mokslu Universiteto Ligonine Kauno Klinikos
ICS-HUB	Hospital Universitari de Bellvitge
UMFCD	Universitatea de Medicina si Farmacie Carol Davila din Bucuresti
CHUC	Centro Hospitalar e Universitario de Coimbra E.P.E.
APHP	Assistance Publique – Hôpitaux de Paris
MUMC	Maastricht Universitair Medisch Centrum

Abbreviations

CFIR	Consolidated Framework for Implementation Research
COVID-19	Coronavirus Disease-2019
CPG	Clinical practice guideline
D	Deliverable
DRG	Diagnosis-related group
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ERP	External reference pricing
EU	European Union
EU MS	European Union Member States
HPF	Hospital Pharmaceutical Formulary
HTA	Health Technology Assessment
SARS	Severe acute respiratory syndrome
SOC	Standard of care
WP	Work package

Executive Summary

The current analysis identifies factors that could positively (as facilitators) or negatively (as barriers) affect the uptake of FX06 in treating hospitalised patients suffering from mild to moderate symptoms of COVID-19. A literature review was performed to search for determinants in the uptake of hospital drugs across the countries of interest, i.e. countries that take part in the clinical trial of the project. The analysis is performed from a health economic perspective and considers factors that apply to the context of the clinical trial. Relevant factors were grouped at a patient-, prescriber-, medicine-, organisational-, and external environmental level:

- Patient-level factors are mainly subject to results of the clinical trial and the evolving field of COVID-19 treatments and include risk factors, concomitant medication, and alternative treatments;
- Prescriber-level factors relate to 'prescribers' knowledge and continuing medical education, as well as to the existence and use of clinical practice guidelines;
- Potentially relevant factors at a medical level pertain to clinical evidence and the innovative character of the medicine;
- At an organisational level, the type of ownership, size, and geographical location of hospitals are deemed relevant to the predefined scope, as well as the use of hospital pharmaceutical formularies;
- Determinants of the uptake of new medicines in the external environment entail the application of horizon scanning activities, the existence of conditional reimbursement regulations, price levels, and market size in a country.

Based on the factors identified, several practical recommendations have been made to explore future actions in the WP and to guide the design of the health economic analysis. It is recommended to gain access to and use patient-level data instead of group-level data from the clinical trial. By this, individual factors can be incorporated into the model. Next, it is recommended to generate an overview of comparators, including the actual use of each treatment and the costs per country. Moreover, in-depth research on factors identified in the current analysis and in former and future analyses (D7.1 and D7.3) is of value to gain insight into the degree of transferability of the health economic analysis across countries.

1 Introduction

1.1 Background

Market access to new medicines entails a series of activities, generally starting with initial evidence generation, followed by reimbursement and price regulation, to instant monitoring and evaluation of the pharmaceutical. The regulatory steps needed between marketing authorisation and implementation in clinical practice across several European countries have been described in the former deliverable (D7.1) of WP7. Once a new medicine has been granted marketing approval, it may take a considerable amount of time before the product becomes available on the market. In Europe, the average time to availability (defined as days between centralised marketing authorisation and inclusion into the reimbursement list) of all types of medicines takes over 500 days. This period, however, highly varies across countries: from 133 days in Germany to 899 days in Romania [2]. Given the non-negligible differences in financing, resources, and coverage of healthcare across European Member States (EU MS), inequal time to availability may not seem surprising. Nonetheless, any delay in the implementation of new, cost-effective medicines may affect improvement in the quality and efficiency of care.

Even when a positive reimbursement decision has been made, the actual use of medicines that are to be used in a hospital setting is not necessarily guaranteed. As described in D7.1, individual public hospitals decide on a case-by-case basis on the inclusion into their pharmaceutical formularies in most of the considered countries. Decentralised implementation at the level of healthcare organisations may also affect the smooth adoption of new evidence-based therapies.

Due to the complexity of medicine introduction, there is no single answer to the root cause of delayed uptake of new medicines. Along the implementation pathway, several stakeholders are involved, each with their own view on the pace and funding of medicine introduction. Reimbursement decisions on medicines, therefore, require a comprehensive approach which balances competing interests, such as innovation for unmet medical needs, universal and equitable access to healthcare, and financial sustainability for health systems. Bearing in mind that healthcare costs continue to rise while resources remain limited, healthcare payers need evidence-based arguments to justify their spending choices. Apart from financial considerations, there may be other barriers to the uptake of new pharmaceutical therapies, which could vary between countries, depending on, for instance, population and clinical practices.

1.2 Purpose and scope

After the comparative overview provided in D7.1, the current deliverable identifies factors that could positively (as facilitators) or negatively (as barriers) affect the implementation of FX06 in the treatment of hospitalised patients suffering from mild to moderate symptoms of COVID-19, and how these may differ between participating countries. These factors are extracted from both scientific and grey literature. Additionally, recommendations on how to benefit from the value of facilitators and how to effectively address barriers or mitigate their consequences are discussed, and how to account for this in the health economic analysis.

With 'today's knowledge, the impact of some factors can be deemed positive or negative in advance, whereas the impact direction of other factors can hardly be estimated since these will be dependent on i) the outcome of the clinical study of the COVend project (the IXION trial), ii) new insights into the clinical field of COVID-19, iii) the environmental context at the time of implementation, etc. Rather than a detailed assessment of relevant barriers and facilitators, the current analysis entails the identification of implementation factors and tries to understand and explain these determinants descriptively.

The analysis is focused on factors that are relevant from a health-economic perspective, leaving aside factors related to legal, ethical, cultural, and political issues, and pragmatic issues, such as logistics. Also, the analysis considers factors that apply to the context of the clinical trial. To concretise, the scope is narrowed to medicines that are used in secondary care or as a specialist-only pharmaceutical, ruling out factors related to treatments in, for example, primary care. Furthermore, where applicable, the lens is directed towards those countries that take part in the IXION trial, i.e. France, Germany, Italy, Lithuania, The Netherlands, Portugal, Romania, and Spain.

1.3 Theoretical framework

In implementation science, several frameworks have been applied to group factors affecting implementation. Commonly used constructs have been structural-, organisational-, provider-, and innovation-level factors, also known as the Consolidated Framework for Implementation Research (CFIR) [3, 4]. The comprehensive, pragmatic framework has more recently been used and extended by patient-level factors [5], and has been adopted in a recently published systematic review on barriers and facilitators to the uptake of new medicines into clinical practice [1]. Determinants of medicine uptake in the review of Medlinskiene *et al.* were grouped into patient-, prescriber-, medicine-, organisational-, and external environmental levels (see Figure 1).

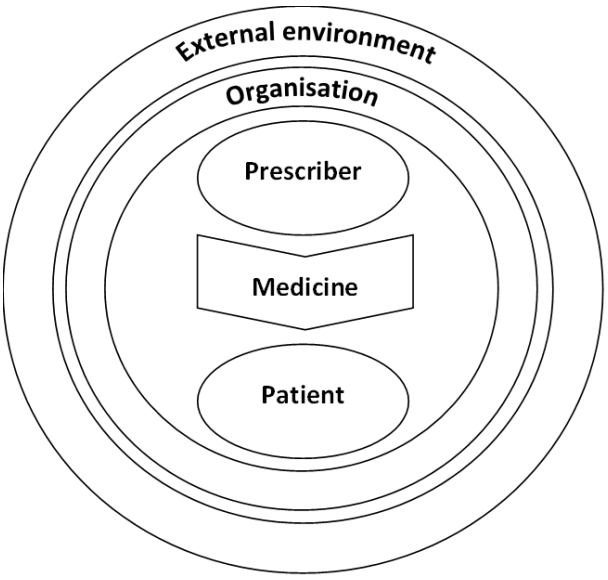

Figure 1 Five levels of determinants in the implementation process of prescription drugs. Source: Medlinskiene et al. [1].

The factors identified in the systematic review were used as a starting point, though the review covered a broader scope than the current analysis does. Each factor is therefore assessed on its potential relevance to the current context, based on a reasonable relationship to the current knowledge of FX06 in the treatment of hospitalised COVID-19 patients. Furthermore, some country-specific factors were identified that could either impede or facilitate the efficient implementation of innovative treatments. All relevant factors that could impact the uptake of FX06 are discussed in the following section.

2 Factors in the implementation of FX06 in COVID-19 care

This chapter explores potential barriers and facilitators to the uptake of FX06 as an innovative drug against COVID-19. The factors derived from the literature are discussed on their relevance to *inter alia* financial considerations, clinical practices and policy aspects at the level of healthcare organisations and jurisdictions when implementing FX06.

2.1 Patient

Apart from the epidemiologic situation of SARS-CoV-2 and the related medical need for new effective treatments at the time of the market introduction of FX06, patient-level factors are mainly related to a 'patient's health status rather than factors related to demographic features and socio-economic status. The health status of hospitalised patients includes, but is not limited to, aspects like comorbidity, polypharmacy and response to previous lines of therapy. Whether these factors enhance or diminish the use of FX06 over alternative treatments is dependent on:

a. risk factors of disease progression;
b. medication use profiles and interactions with concomitant medication;
c. the actual treatment regimen for hospitalised COVID-19 patients.

2.1.1 Risk factors

Relevant risk factors and their relation to the effectiveness of FX06 will be identified as part of the COVend project. Predictive and prognostic factors will be investigated in WP4, in which molecular changes in the pathological context are analysed. In combination with patient characterisation analyses in WP6, these data will provide knowledge on the impact of patient characteristics on the response to FX06 treatment. Other studies have found several patient characteristics, such as age, comorbidity, vaccination status, and immune status, that independently impact the risk of disease progression in Omicron-infected patients [6-8]. Considering all relevant risk factors, certain patient populations at high risk of disease progression could be identified, which reveals the clinical need for effective treatments that prevent disease progression in such populations.

2.1.2 Concomitant medication

Any pharmacodynamic interaction will likely influence the uptake and prescription rate of the drug as well. Thus far, safety and toxicology studies of FX06 raised no concern about potential risks to humans (see e.g., D2.4: 2-weeks toxicity and toxicokinetic report). However, the risk and impact of drug-drug or drug-food interaction are still unknown. To reveal safety events of interest, subgroup analyses on concomitant medication will be performed as part of the IXION trial [9].

2.1.3 Alternative treatments

Current therapy options for hospitalised patients with mild to severe symptoms of COVID-19 are variable. Guidelines on COVID-19 treatments are still in their early stages today, and treatment strategies may differ on a national basis. By the end of 2022, only a small number of therapeutic agents

were recommended by international guidelines, including the corticosteroid dexamethasone, IL-6 receptor blockers Tocilizumab/RoActemra® and Sarilumab/Kevzara®, and the antiviral agent Remdesivir/Veklury® (see Table 1 for newly authorised pharmaceuticals) [10]. Whether treatment response to earlier interventions will impact the implementation of FX06 is mainly dependent on the position of FX06 within the existing treatment regimen, which may also be dependent on a 'patient's indication and the relative safety of FX06 (see also 2.3.1). In general, new treatments could be placed into initial (first-line) or subsequent (second-line, third-line) treatment and would cause a substitution or expansion of existing treatment options or would be combined with current treatments.

Table 1 EMA registered treatments for COVID-19 until January 2023.

Brand name	INN	Drug group	ATC code	Way of administration
Evusheld	Tixagevimab / Cilgavimab	mAbs	J06BD03	subcutaneous
Paxlovid	Nirmatrelvir and ritonavir	antiviral		oral
Xevudy	Sotrovimab	mAb	J06BD05	intravenous
Regkirona	Regdanvimab	mAb	J06BB	intravenous
Ronapreve	Casirivimab/imdevimab	mAbs	J06BD	intravenous or subcutaneous
Veklury	Remdesivir	Antiviral		intravenous
RoActemra	Tocilizumab	mAb	L04AC07	intravenous
Kineret	Anakinra	anti-inflammatory	L04AC03	subcutaneous

ATC: Anatomical Therapeutic Chemical; EMA: European Medicines Agency; INN: International Non-proprietary Name; mAb: monoclonal antibody. Source: EMA [11].

2.2 Prescriber

2.2.1 Knowledge

At the level of prescribers, the implementation success of FX06 is mainly thought to be related to 'prescribers' knowledge. Prescribers that experienced the adoption of new medicines in the past would be more likely to adopt other new therapies. Furthermore, knowledge held by prescribers of the new medicine and continuing medical education on novel treatment options could encourage the uptake of new therapies. Interaction and dialogue between physicians and pharmacists within and between organisations were found to be crucial in the diffusion of new treatments [1]. Moreover, direct pharmaceutical marketing of new medicines to prescribers and indirect marketing using advertisements in journals and at events could influence prescribing decisions. However, an excessive amount of new information might hamper its implementation, as it would be conceived as a marketing offensive rather than a dissemination of scientific information. A considered exposure to current research and treatment trends in the field of COVID-19 could thus shape awareness in prescribers of the existence and clinical features of FX06.

2.2.2 Clinical practice guidelines

The presence of local, national, or international clinical practice guidelines (CPGs) could also affect the prescription rate of novel therapies. The position of FX06 in the treatment arsenal for COVID-19 patients would be ensured after recommendations have been made in CPGs. Although implementation would likely be delayed if no CPG is available for the clinical scenario, it is questionable whether CPGs have been broadly implemented and are evenly used across European countries. There

might be an unequal implementation of new CPGs between high-income countries and low- and middle-income countries due to the inability of the latter to fund the latest therapies. Further, mandatory use and transparent processes to evaluate the scientific evidence used to develop clinical guidance were found to be inconsistent across Europe [12]. Once included in a CPG, though, several barriers to non-compliance to CPGs can be identified at the level of prescribers, including time pressure, fragmented care, and case complexity [13].

2.3 Medicine

2.3.1 Clinical evidence

Essential factors that affect the implementation of FX06 in clinical practice are its relative effectiveness and safety, which will result from the clinical trial and subsequent benefit-risk assessment. As the economic value is represented by the increments in costs and effects of FX06 against one or more comparator strategies, the effectiveness of comparators is at least as crucial in the analysis. Several antiviral treatments may (have) become irrelevant as a comparator strategy, due to a reduced neutralising effect against emerging strains of SARS-CoV-2 [14]. If patients will no longer benefit from these treatments, options in the portfolio of COVID-19 prophylactics and therapeutics will reduce, which semphasises the need for other treatments to prevent COVID-19 patients from disease progression.

As stated before, FX06 was found to have a benign safety profile in pharmacology and toxicology studies. The safety profile will be investigated further in the clinical trial and benefit-risk assessments. Furthermore, the actual impact of 'FX06's favourable safety profile is dependent on the safety profile of alternative treatments. For instance, there are some concerns with potential side effects and contraindications of systemic corticosteroids like dexamethasone in patients with diabetes or immunocompromised patients [10]. Similarly, the incidence of serious adverse events in the treatment with tocilizumab and baricitinib is uncertain [10, 15].

2.3.2 Innovation and convenience

At the medicine level, factors like the degree of innovation and ease of use are perceived as essential as well. The discovered mechanism of action against endothelial damage of the synthetically produced peptide induces a therapeutically innovative treatment approach, which could have a positive impact to the uptake of FX06.

Besides an innovative character, the way of administering the drug could impact the uptake of novel treatments. Oral administration is often preferred over parenteral administration due to its non-invasiveness and convenience [16]. As FX06 is a peptide which would be destroyed in the stomach and intestine, the drug will be administered intravenously in its current form. With the emergence of alternative oral treatments, such as Ritonavir-Nirmatrelvir/Paxlovid® and Molnupiravir/Lagevrio®, the route of administration could impede the clinical use of FX06, although the target group of both oral drugs seems to differ from that of FX06 [11].

2.4 Organisation

2.4.1 Ownership status

Considering increasing healthcare costs and scarce resources, while hospitals may have different financial incentives to choose certain treatments for specific groups of patients, the type of ownership of an organisation may affect the uptake of novel treatment options. Ownership status can be subdivided into publicly-owned hospitals (owned by the government or a public corporation) and privately-owned hospitals (owned by a private unit, whether or not for profit). All except one of the countries of interest have both publicly and privately owned hospitals: in the Netherlands, all hospitals are under private (not-for-profit) ownership (see Figure 2**Error! Reference source not found.**) [17]. The review of Medlinskiene et al. reported contradictory results regarding the effect of the type of hospital ownership on the uptake of new medicines. However, studies suggesting hospitals in the private sector were more likely to implement new medicines outnumbered studies that found the opposite.

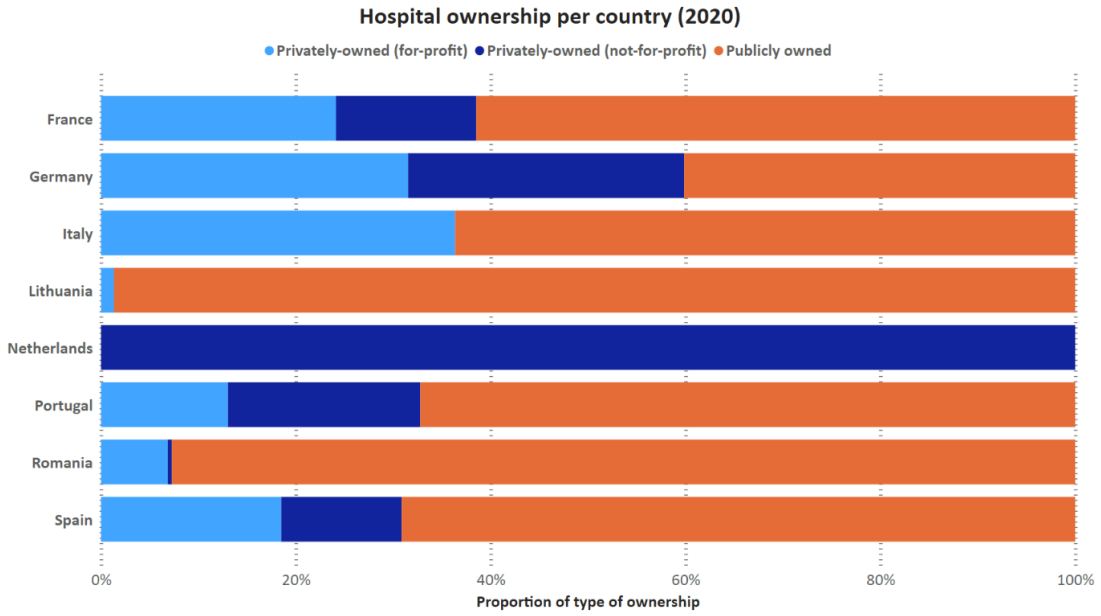

Figure 2 Proportion of type of ownership per country, based on the number of hospital beds in 2020. Source: Eurostat [17].

2.4.2 Hospital size

The size of a hospital should be considered a relevant factor as well since a high prescribing volume could influence implementation regarding efficient purchasing and hospital management strategies. Healthcare organisations with strong market power generally have strong bargaining power, which could impact the time and outcome of a negotiation with pharmaceutical companies on the purchase price on the one hand, and with insurance companies on the insurance price on the other hand. However, when the costs of FX06 is included in the lump sum of a (new or existing) Diagnosis-related Group (DRG), the time and outcome of price negotiations would likely have less impact on

implementation than compared to a situation where the costs of treatment fall outside DRG-payment (see also D7.1).

2.4.3 Location

Another factor at the organisational level deemed relevant to the adoption of new medicines is the location of a hospital within a country. Though marketing authorisation and reimbursement status are uniformly valid throughout all jurisdictions of interest, funding and prescribing of new medicines are less straightforward for countries with strong regional autonomy, like Spain and Italy. In these countries, the regions oversee resource allocation, budget decisions, and the procurement of medicines. Although regions have no legal right to deny access to medicines with a national reimbursement status, they can discourage or incentivise use in clinical practice. Consequently, regional inequalities can impact the successful uptake of a new therapy in these jurisdictions.

2.4.4 Local formulary decisions

As has been described in D7.1, the actual use and funding of new reimbursable medicines are dependent on local formulary decisions, i.e. inclusion into a hospital pharmaceutical formulary (HPF). HPFs might constrain the implementation of novel treatments, as prescription and use of new medicines that are not included in the HPF need a 'prescriber's motivation concerning the necessity and added value over already included therapeutic options. Whether this applies to the context of FX06, mainly depends on existing alternative treatment modalities against COVID-19.

2.5 External environment

2.5.1 Horizon scanning

Several factors at the level of the external environment are related to national reimbursement policies and processes. Chief among these policy-related factors in the adoption of new medicines is the existence of horizon scanning activity and its level of integration in the healthcare system. Policymakers use horizon scanning to identify and assess new and emerging technologies before or at the time of market entry. The systematic identification of new, possibly innovative medicines enables them to prepare for evidence-based decision-making and prioritisation. Of the limited number of countries that do use horizon scanning, some use it in a systematic way (e.g. Italy, the Netherlands), whereas others have less comprehensive horizon scanning activities (e.g. France) [18].
Besides national horizon scanning activities, a cross-national collaborative system called International Horizon Scanning Initiative (IHSI) was established in 2019, which currently consists of organisations from eight countries (Belgium, the Netherlands, Denmark, Ireland, Norway, Portugal, Sweden, and Switzerland). The IHSI, as an independent entity, identifies new pharmaceuticals in different clinical areas (including infectious diseases), tracked from various sources, after which promising pharmaceuticals will be highlighted for further investigation [19].

2.5.2 Conditional reimbursement

Besides horizon scanning, conditional reimbursement can facilitate the implementation of new therapeutical options. Conditional reimbursement is a policy instrument that is used in different forms by a small number of EU MS [20] andit is aimed to sminimise delay in the market entry of innovative medicines, in which a decision on healthcare allocation is based on limited evidence regarding effectiveness and cost-effectiveness. Medicine expenses are covered under conditions such as the supply of real-world evidence on effectiveness and costs by the manufacturer. As this policy tool is generally applied to new medicines with a high budget impact, its relevance in the implementation of FX06 would mainly depend on the estimated financial impact at a country level.
Furthermore, some countries apply policies to fasten the process of reimbursement. In Italy, authorised medicines can be marketed as class C non-negotiated drugs at the expense of hospitals or patients before a reimbursement decision by the competent authority, and in the Netherlands, a pilot has been started to run the reimbursement procedure parallel to the process of marketing authorisation [21, 22].

2.5.3 Price levels

Delayed implementation of new pharmaceutical products is also related to a 'country's economic situation, including income level. As already mentioned in section 2.2.2, in the context of CPGs, a relatively low national income per capita likely has a negative effect on the launch of new medicines. Pharmaceutical companies tend to launch medicines first in countries with high prices on medicines, and even avoid or extend negotiations in countries with less ability to pay for the product [23]. A policy tool to mitigate price differences is external reference pricing (ERP), in which countries set a price of a pharmaceutical product based on a benchmark of prices of the same product in reference countries. However, ERP is mainly applied for outpatient medicines [24]. Because FX06 will be used in a hospital context, ERP is not considered of direct importance to the current context.

2.5.4 Market size

The effect of income level on the implementation of new pharmaceuticals is closely related to the market size (i.e. patient volume) in a given country. In line with the concept of economies of scale, pharmaceutical companies are more prone to start marketing in countries with a relatively large sales volume. This reduces the time to market access of new pharmaceutical products in countries with a large healthcare market, although the opposite is true for countries with potentially smaller revenues [25]. Market size is related to the epidemiologic situation and the presence of subpopulations based on risk factors, as described in 2.1.

3 Recommendations to WP7

Based on the factors raised in the former chapter, several practical recommendations can be made to explore future WP7 actions and guide the design of the health economic analysis.

3.1 Patient level data

The factors described in 2.1 underline the added value of using a patient-level model instead of a cohort-level model. Estimating the outcomes for patients modelled individually makes a model more flexible and allows for the incorporation of individual factors that relate to the specific context. Since UMCG initially would not receive trial data at a patient level, it consequently will request access to spseudonymised patient data of the 'trial's electronic Case Report Form (eCRF). Clinical patient data enables the incorporation of several risk factors, like current drug intake and comorbidity.

3.2 Comparator overview

Cost-effectiveness is a relative concept, meaning that the ratio of incremental costs and effects of the intervention under study against the comparator intervention(s) is calculated to represent the economic value of the studied intervention. As FX06 will be administered in addition to standard of care (SOC), the definition of SOC is important for the comparator arm. IXION data will become a valuable source of information to determine the SOC, which likely consists of a mix of treatments. Today, the COVID-19 prophylactics and therapeutics portfolio has expanded since the pandemic's onset, though its evidence base is still limited. It is recommended to generate an overview of medicines currently used in clinical practice across the countries that are considered in the economic evaluation. Subsequently, each alternative intervention should be assessed to its potential as a reference case to FX06. As SOC may differ per country and healthcare organisation, it is recommended to retrieve the actual use of each treatment, as well as the costs of SOC per country. The overview of potential treatments for the comparator arm will be the subject of the next deliverable, D7.3.

3.3 Transferability of economic values

Even though the IXION trial is a multinational study, and clinical and biological effects are expected to be rather homogeneous across countries, economic data from the study countries may be less generalisable in a country-specific decision context. As mentioned in the former chapter, economic circumstances, and differences in healthcare systems, clinical practices, etc., could impact the degree of transferability of the health economic analysis outcome across Europe, let alone outside Europe. Consequently, transferability impacts the speed of assessment, thereby affecting the widespread uptake of COVID-19 treatments. It is therefore deemed highly important to design a flexible model, apart from the ability of sensitivity analyses. End users of the model should be able to adjust the model structure to align it to the actual clinical pathway of hospitalised COVID-19 patients. This will involve, among others, integrated loops within or between healthcare facilities (e.g. hospital care and rehabilitative care), and time dependency on health status. Thus, a comprehensive understanding of different health systems in the context of COVID-19 care is required, for which the current deliverable, as well as the former and next deliverable of WP7, are all preparations to construct a health economic

model that accounts for major differences across healthcare settings of interest. Moreover, when considering a health economic analysis from a societal perspective, differences in the quantification and valuation of economic productivity across jurisdictions should be clarified. Productivity loss is associated with issues like taxes, labour market constraints, wages, etc., which are all country-specific issues. Despite several challenges to incorporating economic productivity in multi-country health economic analyses, it captures part of an 'intervention's consequences outside the healthcare sector, which is essential to decision makers considering the broad allocation of resources across the population. Hence, in addition to the outcome of the deliverables, more in-depth research would be useful, focused on dynamic parts of the health economic model.

3.4 Incorporating patient preferences

Alignment of patient preferences with clinical and economic evidence is gaining importance in Health Technology Assessment (HTA), because of the increased focus on patient-centeredness of care. However, in the situation of the current project, the essence of patient preferences in the economic evaluation may be rather premature. Usually, patient preferences are explored and elicited in a more advanced stage of HTA, after the benefits and risks between alternative treatments have been appraised [26]. Again, treatment choices are limited for patients who are hospitalised because of severe COVID-19 thus far. Nevertheless, incorporating patient preferences within or beyond the utility value in the health economic analysis could broaden the added value of FX06 against existing alternatives and may therefore be worthwhile to investigate further as COVend advances.

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