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Coordinating Research and Evidence for Medical Devices

Publication on early-phase clinical studies of high-risk medical devices

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Acronyms and abbreviations

CA	Competent Authority
CORE-MD	Coordinating Research and Evidence for Medical Devices
EU	European Union
IDEAL	Idea, Development, Exploration, Assessment, Long term study
MDR	Medical Device Regulation
NB	Notified Bodies
RCT	Randomized Control Trial
SMEs	Small & Medium Size Enterprises

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Executive Summary

The CORE-MD project seeks to address the challenges of providing appropriate clinical evidence to support the process of evaluating medical device performance and safety under the EU Medical Device Regulation. This legislation aimed to standardize and improve the level of clinical evidence required of medical devices, particularly higher risk devices. However, the regulation does not set out specific procedures to be followed in collecting and evaluating evidence but instead creates a set of requirements (such as improved post-market surveillance studies) which could be met in a number of ways. The aim of CORE-MD was to examine the current state of clinical evaluation of devices within the EU system and to propose ways of improving and standardizing this activity across the EU. The research consortium set itself four main objectives to achieve this aim, each to be accomplished by a Work Package:

1. To produce an authoritative and comprehensive systematic review of the methodology of clinical trials and investigations that have been used to evaluate high-risk medical devices
2. To review and recommend alternative designs of studies that can be used to investigate new high-risk medical devices, and to create a hierarchy or matrix of approaches
3. To develop methods for aggregating data from real-world sources and registries across the life-cycle of high-risk medical devices, including reports from patients
4. To implement methods for networking between academic centres and different medical specialties involved in studies of high-risk medical devices, and with notified bodies, regulators and manufacturers, so that they can share experience and best practices and develop collective scientific expertise within the EU.

This report is the main output of Task 2.1, which forms part of Work Package 2. The majority of the work of the CORE-MD project comprises either summarizing and collating evidence about the methods currently in use, or improving integration of data streams and co-operation between involved entities. Work Package 2, however, focuses on the (arguably more creative) task of assessing the potential of new evaluation methodologies which might make clinical evaluation more effective, faster or cheaper. Of particular interest in this regard was the IDEAL Framework, which proposes an integrated evaluation pathway for complex physical health interventions based on a life-cycle approach. Application of the IDEAL Framework to medical devices was first proposed in 2016 [1], and a description of how the IDEAL recommendations mapped onto the requirements of the MDR was published in 2012[2], but there is little practical experience in using IDEAL to develop clinical evidence for CE marking purposes. The aim of Task 2.1 was to develop a series of case studies in which innovators worked with the IDEAL Collaboration to prepare clinical evidence plans using the IDEAL recommendations in order to study the potential value of IDEAL and the facilitators and barriers in the current system which might influence its potential for widespread adoption.

With the help of the CORE-MD project team, invitations to participate were sent to members of the EFORT and ESC clinical groups who were actively developing devices for CE marking, and to other groups who contacted the IDEAL Collaboration in response to its Advisory Service. Overall, a total of 22 groups were

approached of which 18 entered into preliminary discussions where the IDEAL framework and its potential for application to their evidence development plans were explained and discussed. Those innovators who wished to, then worked with IDEAL advisors to develop proposals for appropriate clinical studies and discussed these with their support teams. Support and advice were offered by the IDEAL team and liaison was maintained during the evidence development process. A questionnaire (**Error! Reference source not found.**) was sent to all innovator partners at least 6 months after the initial planning meeting, to understand initial impressions and experiences of using IDEAL methodology in this context. A further 3 months later a series of semi-structured interviews were conducted with those innovators who agreed to this, whilst all groups were requested for information on their practical progress in developing clinical evidence and using IDEAL to do this.

The results of the Questionnaire survey show that the validity and applicability of the IDEAL Recommendations were rated very highly, and most innovators did not find them difficult to understand or apply, with only 14% indicating that they were reliant on expert help and advice. Few concerns were raised about the costs and time requirements of IDEAL format studies. However, innovators were concerned about whether regulators, funders and publishers would understand or accept IDEAL. These results were reinforced and fleshed out by the interview study. The main themes identified were the potential benefits of adopting IDEAL for regulatory evidence purposes and the major barrier to using it imposed by lack of transparency about what the Notified Bodies and regulators would find acceptable. Interviewees felt that a standard way of describing innovations based on their stage of evolution through the evidence life cycle would be extremely helpful, allowing developers, notified body and regulation staff and HTA organizations to use a common language. The importance of transparency about the inevitable iterative development steps in device refinement was recognized, as was the need to evaluate therapeutic devices in use in a range of clinical settings, users and patient populations. The IDEAL proposal for evaluation of 'use quality' to measure learning curves and fidelity of delivery was also considered valuable.

Concerns about the likely response of Notified Bodies to a novel form of clinical evidence presentation proved very influential in deciding actual behavior. Only one of the 12 innovator groups from the CORE-MD project organisations who discussed collaboration actually used an IDEAL format study in their submission for regulatory approval, although most claimed to have used IDEAL at some point in their studies. Several reported that team members or supporters were concerned about the risk that the IDEAL studies would not be understood or accepted as valid by Notified Bodies or regulators. This fear might have been allayed if discussions with Notified Bodies over the development of clinical evidence packages could have taken place, but these are currently forbidden under EU "consultancy "regulations.

In conclusion, the study provided strong qualitative evidence that device developers see significant potential benefits in using the IDEAL recommendations for the development of early-stage clinical evidence suitable for CE marking applications, and would be very happy to use it if it were officially recognized or endorsed as an appropriate methodology by the EU regulatory apparatus. Without this official support, however, most innovators regarded its use as too high risk. These findings raise concerns

about the lack of transparency and resistance to change within current EU systems for device evaluation based on Notified Bodies. The inability of innovators to discuss with Notified Bodies what types of studies would be acceptable results in a default position of continuing with approaches used in the past, which effectively locks out methodological innovation. This is likely to have adverse consequences in terms of both competitiveness and safety for the EU system.

1 Introduction

1.1 Evidence for Device Regulation in the European Union and the MDR

The European Union recognizes that it has a responsibility for public health at the community level in certain respects. One of these relates to regulation of medicinal products to ensure their safety and effectiveness. The European Medicines Agency has a clearly defined role in approving pharmaceutical products, but the authorization of marketing for medical devices is delegated to a network of commercial "notified bodies" which carry out "conformity assessment" rather than licensing. Dissatisfaction with the performance of the previous European Medical Device Directive led to the development of the Medical Device Regulation [3]. This took important steps to improve the evidence supporting new devices. Higher risk implantable devices can no longer be approved without direct clinical evidence, on the basis of "equivalence", except in very specific circumstances. The expectations on the level of clinical evidence supplied for the higher risk categories of device have been raised, and a requirement for specific post-marketing surveillance studies has been introduced. All devices are required to refresh their evidence portfolio every 5 years.

Whilst these steps addressed some clear risks to public health, the Regulation did not change the infrastructure for conformity assessment based on the notified body system, nor did it set out either methodological principles for the development of clinical evidence or a clear threshold for the evidence required for approval. Given the heterogeneity of the health systems and interpretations of the MDR in the member states, application of the MDR's general principles is likely to vary considerably, resulting in major differences in approvals, and increasing potential risks to public health.

The MDR seeks to provide 'a robust, transparent, predictable and sustainable regulatory framework for medical devices which ensures a high level of safety and health whilst supporting innovation', but without supporting advice on methodology, it is unlikely that this aim will be realized. The problem is exacerbated by rules on "consultancy" for Notified Bodies which prevent them from advising client companies on study design, and commercial confidentiality rules which screen the details of clinical investigations and inhibit transparency. Bereft of other sources, innovators often rely on paid consultants to help them design their clinical investigations but have no good way of gauging the quality of the advice provided. The call to which the CORE-MD consortium responded was one which sought both a review of current methodology for developing and analyzing clinical evidence for devices and advice on methodology gaps, novel methods, and which methods would be most appropriate at which stages in evaluation. The CORE-MD proposal was to "review methodologies of clinical investigations, advise on study designs, and develop recommendations for aggregating clinical data from registries and other real-world sources." As part of this, recognized weaknesses in the current methods for developing early clinical evidence were to be addressed.

1.2 IDEAL and the development of early clinical evidence for devices

Medical devices, particularly implantable therapeutic devices such as pacemakers or orthopaedic implants, are recognized as having properties which make clinical evaluation more challenging than that for Pharma products. They share this peculiarity with other physical interventions such as surgical procedures, radiologically and endoscopically guided treatments and complex process interventions like accelerated recovery programmes. The common characteristics which define this group of interventions include the need for iterative improvement during early clinical use, great dependence of outcome on the quality with which the intervention is applied – often related to the level of acquired operator skill - and difficulties in both blinding and equipoise (for both therapist and patient). Randomised controlled trials of interventions in this category of treatments are smaller, lower quality and less likely to be completed than RCTs in pharma or allied disciplines[4].

In 2009 the IDEAL Framework was published, which described the life-cycle of these complex treatments in 5 Stages [5]. The stages follow each other in a predictable sequence, and each is focused on a specific question which needs to be answered if progress to the next stage is to proceed securely. The IDEAL Recommendations provide guidance on how study designs can be developed to answer the key question at each IDEAL Stage, and using the recommendations at each stage results in an integrated evaluation pathway analogous to the Phase 1 - Phase 4 pharma pathway[6]. More information on IDEAL is shown in Table 1and Figure 1.

Table 1. The stages of the IDEAL Framework, describing the evaluation life cycle of complex interventions

IDEA (Stage 1)	DEVELOPMENT (2A)	EXPLORATION (2B)	ASSESSMENT (3)	LONG TERM STUDY (4)
Initial report	"Tinkering" (rapid iterative modification)	Technique now more stable	Gaining wide acceptance	Monitoring late and rare problems, changes in use & quality of surgical performance
Innovation may be planned, accidental or forced	Small experience from one centre	Replication by others	Considered as possible replacement for current treatment	
Focus on explanation and description	Focus on technical details and feasibility	Focus on adverse effects and potential benefits	Comparison against current best practice (RCT if possible)	
		Learning curves important		
		Definition and quality parameters developed		

In the early stages of clinical evaluation, the recommendations for **IDEAL Stage 2a** suggest transparent sequential reporting of uncontrolled case series, highlighting changes to device, technique of use or indication, and studying how outcomes are affected until stability is achieved.

In **Stage 2b**, prospective collaborative cohort studies involving multiple centres allow evaluation of operator learning curves, resolve controversies about outcomes in patient subgroups or technique variants, and provide a "real world" effect estimate.

Stage 3 is when definitive "pivotal" studies of comparative effectiveness occur, and

Stage 4 deals with long-term surveillance to detect late or rare events.

The IDEAL proposition is that such preliminary studies increase the probability of a successful RCT, but they also provide evidence about safety and efficacy highly relevant to the needs of pre-market evaluation for high-risk devices. The ways in which the IDEAL Recommendations could support evidence requirements within the MDR were explored in a position paper in 2021.[2]

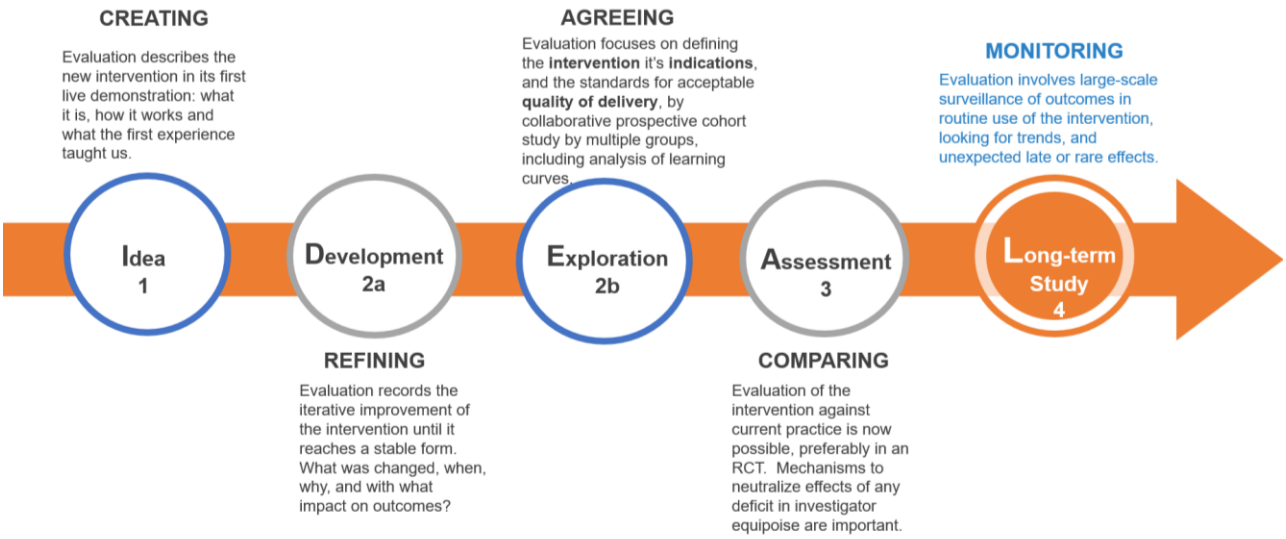

Figure 1. The IDEAL Recommendations, describing how stage-specific approaches can create an integrated evaluation pathway for complex interventions

1.3 Exploring the value of IDEAL in improving clinical evidence in the MDR

The IDEAL Framework is therefore a novel and potentially important source of guidance for device innovators preparing clinical evidence portfolios for regulatory approval. However practical experience with using IDEAL in this context is lacking. We proposed to work with innovators in a series of case studies

in each of which a protocol for clinical investigation would be co-developed by the innovators and IDEAL Collaboration members.

The IDEAL stages have been shown to map well onto the current steps in clinical evaluation proposed by the MDR[2] (See Figure 2). There are few, if any, other general frameworks available for research methodology in this area. The UK MRC Complex Methodology framework covers similar ground but is more general in its approach and less clearly defined in its terminology and the degree of operational guidance provided[7]. IDEAL therefore represents the best available opportunity to introduce a standard approach to device evaluation based on relevant expertise and sound scientific principles. Since there is no evidence base for using IDEAL in the regulatory evidence context, a first step in exploring its value would be a pilot study of use in some example cases with a qualitative analysis of its potential and the feasibility of integrating it into the existing EU system. The aim of the present study was therefore to evaluate the potential of IDEAL, as a generally applicable framework for designing early-stage studies, to supply a standard language and approach for the evaluation of devices preparing applications for CE marking.

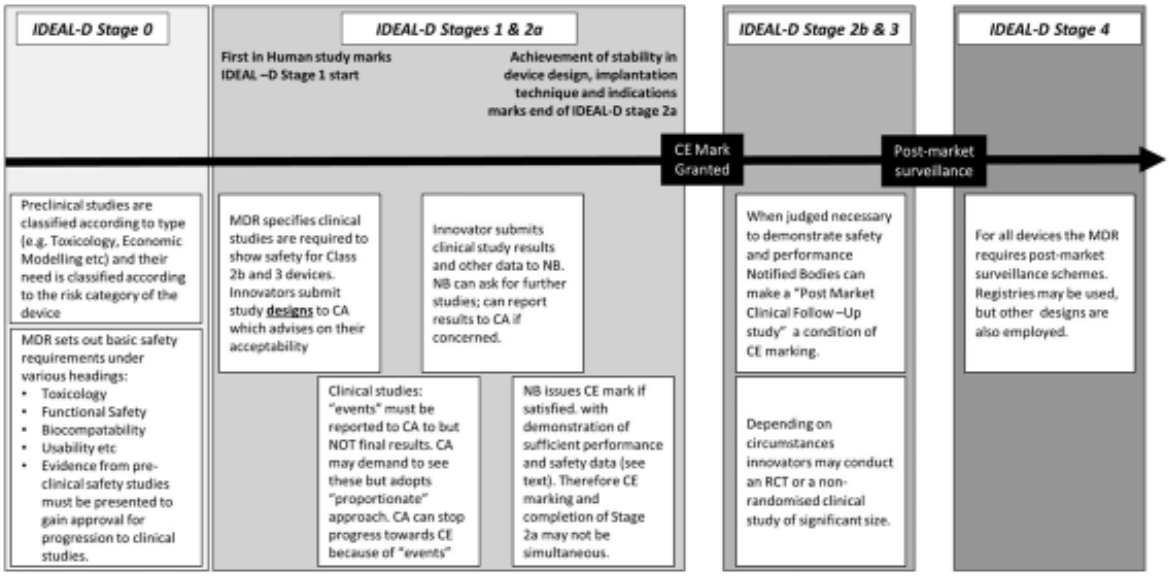

Figure 2. Alignment of the IDEAL stages with progress through the Medical Device Regulation (MDR) system for medical device evaluation and approval [2] .

2 Methods

The underlying theory for this study is that IDEAL correctly describes the life cycle of evolution and evaluation of complex invasive therapies such as operations and implantable devices, and that it provides an optimized approach to designing and conducting clinical studies of new complex interventions to address questions of safety and effectiveness. We sought first to find colleagues and groups working on developing evidence for new invasive devices and to recruit interested groups to take part in the study. We then organized video meetings with each group to explain the IDEAL Framework, the nature of the study and how it would affect their current plans for evaluating their devices. After this we engaged with the groups to determine how IDEAL recommendations could be integrated into their evaluation plans. We sent out a questionnaire after 6 months to get initial feedback from investigators and then completed evidence gathering with a series of semi-structured interviews.

2.1 Recruitment of partners

Working with the lead investigators for CORE-MD (Professors Alan Fraser, Per Kjaersgaard-Andersen and Rob Nelissen), we sent messages to members of specialist professional organisations who were involved with the CORE-MD project (the EFORT group which evaluate orthopaedic implants and the European Society Cardiology), asking for volunteers to take part in the study. We also advertised the study on the IDEAL Collaboration website (www.IDEAL-collaboration.net). We sought expressions of interest from investigators who were working on development of clinical evidence to support an application for "CE marking". We specified that devices needed to have a therapeutic purpose and to be in device risk class IIb or c or III in the classification set out in EU Council Directive 93/42 of 1993. Partners consented to undertake a questionnaire and to consider to be interviewed under the Ethics arrangements approved for the CORE-MD programme. We sent potential participants a description of the study and some explanatory materials about IDEAL and we agreed to sign non-disclosure agreements when requested.

2.2 Development of IDEAL proposals

We developed an understanding of the devices being developed by partners through video meetings and e-mail exchanges, and made suggestions about how the existing plans or future studies could be designed or remodeled to make them compatible with IDEAL. Where investigators were willing to share protocols the IDEAL team sent proposals for revisions to align them more closely with IDEAL. Plans for integrating IDEAL into the protocols were then developed via exchange of e-mails and video calls. We maintained contact with groups by regular monthly e-mail. By the nature of the early clinical evidence required for CE marking, most study plans were suitable for reconfiguration as either IDEAL Stage 2a or 2b studies. The key features of these study types are listed in Table 2. Innovators made their own decisions about their

clinical investigation plans and communicated these to us, with additional video discussions and e-mail exchanges to ensure clarity of understanding of the final plan.

Table 2. The IDEAL Recommendations for design and reporting of Stage 2a and Stage 2b studies.

	IDEAL Stage 2a	IDEAL Stage 2b
Design	Prospective cohort study with sequential reporting and analysis of iterative changes	Collaborative multicenter cohort study with agreed dataset and data definitions
Reporting	Detailed technical description of initial procedure	Achievement of consensus-defined measure of delivery quality, analyzing cases consecutively
Reporting	Detailed description of patient selection criteria	Qualitative analysis of views of patients and clinicians around outcome measures and appropriate comparators for an RCT
Reporting	Description of ALL modifications to procedure, device or indications, when made, and why.	Subgroup results for pre-specified controversies over patient selection and/or technical variations
Analysis	Prospective analysis of all cases reported consecutively, to show relationship of outcomes to changes	Analysis of learning curves, mean effect size and variance (for power calculations for RCT) and signals of outcome differences in prespecified subgroups
Analysis		Consensus discussion of results to determine: • Feasibility of an RCT • Trial question • Comparator • Quality measures • Learning curve completion criteria • Sample size • Patient inclusion/ exclusion criteria • Acceptability of technical variations

2.3 Expert Analysis of Evaluation Plans

We classified the final study plans described to us as:

(a) Compliant with IDEAL recommendations

(b) partly compliant with IDEAL recommendations, or

(c) Not compliant with IDEAL recommendations.

This classification was decided by an IDEAL expert panel, based on whether the study plan achieved the primary goals of either IDEAL stage 2a or 2b studies and the extent to which they followed the key recommendations for each stage [8].

2.4 Feedback by Questionnaire

In order to understand the process by which innovators reached their final decisions over study plans, and specifically the use of IDEAL within them, we distributed a questionnaire to the principal investigators for each device included. The devices included comprised all those whose investigators had agreed to initial contact and discussion of using IDEAL in the design of their clinical studies of devices or operations, whether or not they ultimately did so. The questions were developed and tested by members of the IDEAL Collaboration in informal discussions with a small group of experienced innovators who did not take part in the main study, as they had already achieved CE mark status. The questionnaire was sent to investigators around 6 months after the initial interview in which the nature of their device and their evaluation plans were clarified. A second questionnaire was sent to non-responders where no reply was received within a month, and a further e-mail was sent to any remaining non-responders asking them to let us know if they wanted to respond or withdraw from the study. A copy of the questionnaire is shown in Appendix **Error! Reference source not found.**.

2.5 Semi-structured Interviews and Thematic Analysis

All innovators who were sent the questionnaire were asked whether they would be willing to take part in a semi-structured interview as well. Interviews were all conducted by a single investigator, with support from the Principal Investigator for the first 2 interviews. Interviews are conducted online using Teams software and video/audio recording, after the completion of the protocol for early clinical studies agreed with the IDEAL Collaboration, in the case of innovators who decide to pursue the option of using IDEAL, and 6 months after the first discussion about developing such a protocol in the case of innovators who decide not to use IDEAL or to adopt only some aspects of the recommendations.

The results of the Questionnaire informed the design of the Interview Guide, whose principal aims were to elicit explanations of:

(a) innovator impressions of the IDEAL Framework and its potential value in clinical evidence development for regulatory evaluation of therapeutic devices, and

(b) explanations of the process by which innovators arrived at their final decisions over investigation plans and the use or non-use of IDEAL, including explanation of the factors which influenced their thinking over methodological options.

The interview guide was constructed with a view to exploring the following issues:

- Whether they followed the IDEAL Recommendations for their stage of IDEAL precisely and completely.
- Where this was not the case, why they chose to diverge from the Recommendations.
- Which part of the IDEAL Recommendations they found conceptually difficult to understand or follow.
- Which parts of the IDEAL Recommendations they found impractical or irrelevant to their studies, and why.
- Whether they were influenced in their decision making about using IDEAL by the known or suspected attitudes of other actors such as funding bodies, regulators, professional societies, Health Technology Assessment bodies such as NICE, Journal editors and publishers.
- Whether they were influenced by perceived lack of expertise or support in specific areas of science e.g. methodological help to design IDEAL studies, statistical advice on evaluating learning curves, qualitative research expertise to fulfil the Recommendations in IDEAL stages 2b and 3.

Questions were framed to address the key issues of IDEAL's methodological appropriateness and potential value and which other considerations innovators took into account in deciding whether and how to adopt it. Formal thematic analysis of the interview transcripts is performed, using NVivo software to assist in coding and in identifying themes, which are then characterized through an interpretative explanation of the titles chosen for each theme, alongside illustrative quotes from interviewees.

3 Results

3.1 Partner Recruitment and Collaboration

Our appeals for innovators to work with the IDEAL Collaboration resulted in 22 expressions of interest, 12 from enquiries distributed via CORE-MD partner organizations and 10 from advertisements on the IDEAL website. The nature of the innovator groups and the innovations they were developing varied widely and are summarized in Table 3.

Of the 18 groups who took up the offer of an initial consultation about using IDEAL, four followed the IDEAL recommendations fully or to a large extent, 3 adopted some of them, and 11 did not adopt IDEAL to any significant extent in their development of clinical evidence (Table 3). Some of these latter groups abandoned their projects without developing a clinical evidence submission for regulatory approval, for reasons such as lack of funding, device problems or COVID.

Table 3. Groups invited to collaborate, with devices, progress, use of IDEAL and intentions to apply for CE mark

Lead	DEVICE	Candidate device?	Agreement to collaborate	Use of IDEAL	Preparing for CE marking
DB	Thumb splint for OA	YES	YES	FULL	YES
GD	Knee prosthesis	YES	NO	NO	YES
EG	Cell therapy for knee OA	YES	NO	NO	YES
FB	Hip and knee prostheses	YES	NO	NO	YES
JSH	None	NO	NO	NO	NO
LH	None	NO	NO	NO	NO
PR	None	NO	NO	NO	NO
SJ	None	YES	NO	NO	NO
DK	None	YES	NO	NO	NO

FM	Cardiac Valve repair	YES	NO	NO	YES
TM	Cardiac valve repair	YES	NO	NO	YES
SW	Various	YES	NO	NO	YES
FR	Spinal surgery device	YES	NO	NO	YES
NV	Multimodality neurosurgery guidance	YES	YES	FULL	NO
AG	Neurosurgery automatic biopsy tool	YES	YES	FULL	YES
AO	None	NO	NO	NO	NO
EP	Neurosurgery device	YES	NO	NO	YES
LK	Laser for lichen planus	YES	YES	PARTIAL	NO
JJS	Hepatic trauma rescue device	YES	NO	NO	YES
DA	Auxiliary liver transplant technique	YES	YES	PARTIAL	NO
GF	Microwave colonic polyp detection	YES	YES	FULL	YES
PP	Multimodality neurosurgery guidance	YES	YES	PARTIAL	NO

Blue shading indicates IDEAL Advisory clients, green indicates CORE-MD partners.

3.2 Questionnaire Study Results

The questionnaire revealed strong support for the way in which the IDEAL Framework modelled the development and life cycle of innovation in therapeutic devices, and the description of this process as captured in the IDEAL stages. There was also strong agreement with the concept of proposals for evaluation selected to be appropriate for each stage of the innovation life cycle and broad agreement with the IDEAL Recommendations for the different stages. Comments on the attractions of using the framework included "*seemed a suitable platform to deploy in our trial*", "*gives sensible advices how to design studies about innovative techniques and devices*", and "*clear methodology*".

Most innovators (70%) had little or no experience of using IDEAL before they considered adopting it, but only 20% reported having any difficulty in applying it. All of those who had difficulties were appreciative of the support supplied via the IDEAL advisory service, and felt that it was an important factor in favour of adopting the framework. Questions around potential barriers to using IDEAL included several addressing the potential risks for the use in terms of the time, money and effort likely to be required to complete IDEAL format studies, and others focused on the potential concerns of innovators about the knowledge of IDEAL and attitude to it in bodies and groups whose approval innovators depend on, particularly those involved in device regulatory evidence evaluation both in "competent authorities" and in notified bodies. Respondents generally reported little or no concern that using IDEAL would be more laborious, time consuming or expensive than alternative evaluation frameworks, but were more worried about the attitude and understanding of regulators, journal editors and funding bodies. These findings are summarized in Figure 3.

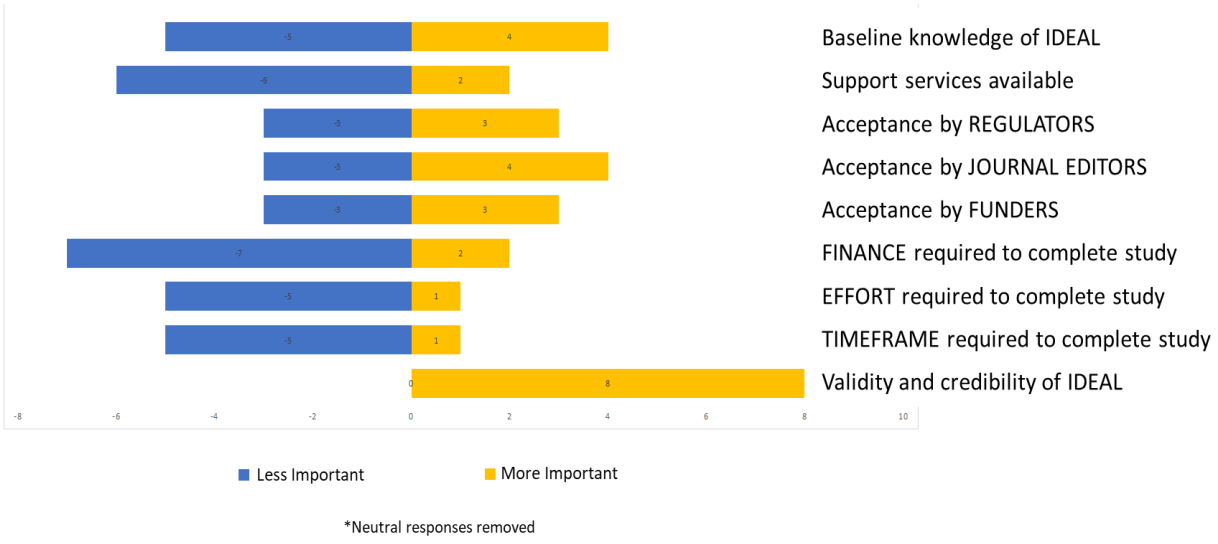

Figure 3. Factors considered important by innovators as potential barriers or facilitators for adoption of IDEAL

3.3 Interview Study Results

Our interviews with innovators are still ongoing at the time of writing, as "saturation" has not yet been reached, i.e. the stage at which qualitative interviews cease to bring out novel information which has not already been surfaced by previous interviewees. We have conducted 10 interviews to date, and although the full thematic analysis awaits saturation, preliminary review of the themes which we have noted is feasible. It is possible that there will be some changes in the final analysis, but the general shape of the themes is already becoming clear.

The four themes which have emerged to date are around the deficiencies of the current system, and the ways in which it is not fit for purpose, the logical coherence and suitability of IDEAL for clinical evaluation of therapeutic devices, its lack of logistical disadvantages and possible logistical advantages, and concerns and hesitation about using it based on perceptions of creating problems with notified bodies or regulators.

The current system is seen as inflexible, and as distorting evaluation by encouraging unsuitable approaches based on pharma studies. Comments from interviewees included:

> *"When you're introducing a new surgical therapy or a device, you can't do what you could do with drug treatments. Like you can't have 200,000 people taking the drug and then taking a placebo in the other arm"*
>
> *"Everything is geared up towards drug development and vaccines and things like that, which is really completely different from introducing a device"*
>
> *"The concept of having to do an RCT on everything just doesn't make sense… But on the other hand, we also can't afford the random introduction that has created so many scandals over the years"*

IDEAL was approved of by interviewees because of its capacity to define where evaluation is within the life cycle, the "fit" between its recommendations and the challenges of clinical research with devices, and the integrated, standardized pathway that it creates. These points were illustrated by comments including:

> *"It was really nice to have these different stages where you can sort of assess each stage. You know, you got your idea originally, but then you consider define each stage really nicely and sort of do it in a sort of gradual stepwise process."*
>
> *"It's a very sensible framework. You start from the beginning where it's first in man and you end up where something's very established and you're following up with long term data and everything in the middle."*
>
> *"The future [for device development] is that the approved bodies or these authorities use the IDEAL framework to help companies that are applying for these CE Marks… to organize the process and to make it more uniform… and confirm that everything has been done properly."*

IDEAL allows new researchers to "be able to categorize where your research fits in a spectrum of evaluation".

Innovators believed that using IDEAL could help reduce the costs of developing regulatory evidence as well as potentially speeding the process of collecting evidence:

"It could save you money.. because it's kind of splitting it up a bit, it's iterative. It is saving money at each stage, which probably makes it easier."

"it's good for funders and they're starting to take that on board. They can identify where the research sits and the reason for that is that the risks involved in delivery and all sorts of things for a research project are highly dependent upon where they sit."

"A lot needs to change in the infrastructure in terms of how those trials (non-CE marked device trials) are run."

The inertia of the current system was identified as a barrier to change – innovators felt that they had little option but to comply with the requirements of the current system even though they did not agree with the approach.

"[IDEAL] makes absolute sense…because what you have [right now] is a sort of regulatory framework which is 'everybody's got their own way of doing things'… and everybody's trying to make everyone else happy, and you have to jump through all these hoops."

"*We need the regulatory authorities internationally to agree. And I personally think IDEAL could be one of the things that could actually be used as a regulatory tool."*

These themes, unsurprisingly, mirror the findings of the questionnaire, but provide greater detail about the attitudes and concerns of device innovators. Several innovators highlighted the risk to innovators working alone or in small or medium size enterprises (SMEs) in taking a novel approach to the development of clinical evidence. Whilst IDEAL appeared to offer potential savings in the time and money needed to develop this, uncertainty about the reaction of notified bodies was a key concern in the absence of a portfolio of documented cases of devices receiving CE marking based on IDEAL-format evidence. A very important factor which worsened this uncertainty was the current prohibition of discussion between innovator and notified body about what would constitute an appropriate set of studies and the study designs used, under "Consultancy" rules. There was widespread agreement that these rules were detrimental to the production of good clinical evidence, because the uncertainty they cause impels innovators to fall back on advice from self-declared "Consultants" who rely on their past success in designing evidence portfolios which supported successful CE marking applications. The methodological sophistication of such bodies varies considerably, and by definition their chief marketing tool is past success – which may not be particularly relevant following the changes due when the MDR is fully implemented and the Notified Body structures are reformed. The Consultancy embargo on discussions

between regulatory evaluator and innovator is in stark contrast to the current policy at the FDA, where early contact and discussion is encouraged. It inevitably results in methodological stagnation, since any innovation cannot have the backing of proven success in the current system. Innovators therefore fall back on the old British proverb “always keep a hold of nurse, for fear of finding something worse”.

3.4 Outcomes: Compliance of final study designs with IDEAL Recommendations

Of 18 innovator groups who agreed to consider using IDEAL in their evidence development, 9 were members of the CORE-MD consortium, working on orthopaedic or cardiac devices, and 9 were groups which contacted the Advisory Service offered by the IDEAL Collaboration. Of the latter, 5 groups were involved in developing evidence for CE marking and 4 were not, whereas in the CORE-MD group 7 were preparing for CE marking and 2 were not. All groups were exploring the use of new technology in clinical studies.

Of the 9 groups identified by the CORE-MD consortium, only one proceeded with the use of IDEAL in developing their clinical evidence portfolio, and it did so fully. Some of the others had not yet applied successfully by the study end, but none of these “pending” applications had indicated interest in using IDEAL in their proposals. In contrast, 6 of the 9 groups not associated with the consortium complied to some extent (3 fully or near-fully, and 3 partially) with the IDEAL recommendations, but only two of the 6 who used IDEAL used it for regulatory evidence purposes, the others using it for research funding applications. Table 3 shows the nature of the innovation for each group, the status of their CE marking application (if known) and the degree of compliance shown with the IDEAL Recommendations after discussion with the IDEAL team.

4 Summary and conclusions

4.1 Purpose of the Workstream

Task 2.1 within the CORE-MD project was focused on "Providing evidence during the early development of high-risk medical devices". The specific purpose of this task was to evaluate the potential of a new methodological framework, IDEAL, in developing evidence appropriate for inclusion in clinical evidence portfolios accompanying applications for CE marking.

IDEAL takes a stage-by-stage approach to the clinical evaluation of complex treatments, and prescribes methodological principles for each stage. The use of a standard framework for developing evaluation methodology has clear advantages for a large international collaboration such as the EU device regulatory system, and could be extremely useful during the implementation of the Medical Device Regulation (MDR), particularly with respect to higher risk categories of implantable and therapeutic devices, for which the MDR sets higher expectations for supporting clinical evidence than existed under the previous regime. The proposal was therefore put forwards that the theoretical advantages of using IDEAL to design studies during early clinical evaluation (the phase during which CE marking is usually applied for) should be tested by developing a suite of case studies on which innovators agreed to consider the use of IDEAL in developing their clinical evidence portfolios.

4.2 Specific Proposals and Actions

The proposal for this task was to identify and enter discussions with a range of innovators who were engaged in, or contemplating, the development of clinical evidence to support the use of therapeutic devices or technology-drive procedures which had not yet applied for a CE mark or, in the small number of cases where the innovation was a procedure rather than a device, had not been the subject of a valid study of comparative effectiveness (normally a randomized controlled trial). Innovators worked with IDEAL Collaboration members to develop a proposal for clinical evaluation based on the IDEAL Recommendations and the innovator group then decided whether to used it, reject it or modify it.

The opinion of the value of IDEAL and the potential barriers to its use in the EU regulatory evidence system was sought in a questionnaire 6 months after each project joined the study. Volunteer innovators underwent semi-structured interviews which were thematically analyzed to understand their perspective better and to look for themes in the views of innovators across a range of project and device types. A review was conducted after 1 year to determine which groups had used IDEAL, and how well their proposals aligned with IDEAL recommendations. For those who chose not to use IDEAL or to use it in partial or modified form, interview questions were directed at their reasons for rejecting or modifying the recommendations.

5 Findings and Conclusions

Twenty-two Innovator groups were approached, and 18 agreed to take part in the study, nine from the CORE-MD group and nine from the group of other innovators who had contacted IDEAL. Seven groups used IDEAL either extensively or partially in applications for CE marks or in other applications such as grant funding. Only one of these was from the CORE-MD consortium, and whilst 4 groups used IDEAL extensively 3 groups used it partially or modified it in a major way.

We have no direct evidence to explain why the non-CORE-MD group were more likely to use IDEAL, but it seems likely that they were more motivated to use it and more positive in their views of it, since they took the initiative by responding to a call on the IDEAL website for expressions of interest, whilst the CORE-MD group were identified by the project leads as active groups who should be approached, so they were not actively seeking methodological help. Questionnaire results and interview comments showed that the impression of IDEAL expressed by the innovators in both groups was extremely favourable in terms of its coherence, validity, suitability for purpose and likely effect on costs, work and time associated with evaluation.

This favourable opinion was balanced, however, by other factors which explained the low rate of uptake of IDEAL in practice, and particularly in the development of clinical evidence for CE marking. Chief amongst these factors was uncertainty about how a novel evaluation framework would be received by regulatory organisations, and specifically by Notified Bodies (although concerns about the attitudes of research funders and journal editors was also raised). Proceeding with a portfolio based on IDEAL methodological recommendations was regarded by many innovators as risky, given the high costs of failure and the lack of information about how regulators might think. This uncertainty could have been relieved if preliminary communication between Notified Bodies and clients about the type of evidence which would be likely to be acceptable could have taken place, but these are currently embargoed under EU consultancy rules.

Our conclusions were that IDEAL appeared to be suitable as a standard framework for developing regulatory evidence, and was approved by most innovators, but that the uncertainty about whether it would be understood or accepted by regulatory bodies, in particularly notified bodies, caused most innovators not to use it. The uncertainty which deterred them was made worse by the embargo on discussions with clients about the nature of evidence which notified bodies would find acceptable under current consultancy rules. At present most innovators, lacking knowledge of what NBs would consider acceptable, rely on third party consultancies whose business model is based on a track record of successful CE marking applications. Essentially this means that new methodology which does not have such a track record is unlikely to be adopted. IDEAL therefore appears to be an exemplar of a potentially valuable methodological innovation which cannot be easily implemented within the EU system because of the lack of transparency for innovators about the nature of clinical evidence which is required. This is a serious problem for EU regulators, as it points to a closed system which effectively locks out methodological innovations which, of necessity, lack evidence of previous success within the current system.

A high-level review of the degree of communication over evidence development proposals permitted between regulators and innovators is urgently needed to correct this problem, which will otherwise prevent modernization of evaluation methods for regulatory purposes, worsening the EU's current deficit in competitiveness in this field. Scientific discourse only functions effectively in an atmosphere of openness and transparency, and the specific issue of communication over evaluation methods between NBs and clients is only one of a number of features of the NB system which are in tension with this prerequisite. The commercial confidentiality agreements with clients which prevent public access to information about the tests performed and their results are also a major drag on successful innovation, because they prevent others from learning about how devices function in different situations until and unless the innovators choose to publish this information. More importantly, this lack of transparency carries with it serious risks of harm to patients if innovators choose not to investigate signals of possible mechanisms of device malfunction short of actual harm, and these signals are not subject to scrutiny from third parties. In the current system even the Competent Authority will not be aware of such signals until an unequivocal safety incident occurs, unless the innovators voluntarily inform them. The need for greater transparency in these two areas suggests that the Notified Body system itself is in need of substantial reform to rebalance the tension between the commercial confidentiality which arguably benefits innovative businesses and the transparency which is fundamental to both effective surveillance of safety and accurate scientific evaluation of device properties.

The preliminary analysis presented in this delivered will be complemented by a publication summarizing the work which is described above. This is awaiting the complete analysis of the interview study, and will be submitted to a peer reviewed journal. Additional publications are expected from the workstream. One of these, a paper co-authored with Dr Tom Melvin, member of the Advisory Board of the CORE-MD project, on the potential for integrating IDEAL into the machinery of the MDR, has already been submitted.

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Appendices

A.1 Innovator Questionnaire on Barriers and Facilitators for using IDEAL

1. Please enter today's date *

2. How did you hear about IDEAL? *

   Internet Search

   Colleague

   Conference

   Journal/Article

   Social media

   Other

3. How did you hear about IDEAL?

   Internet Search

   Colleague

   Conference

   Journal/Article

   Social media

   Other

4. What attracted you to the idea of using IDEAL for your study? *

5. How much baseline knowledge of IDEAL did you have prior to deciding on using the IDEAL framework or not? *

   None

Somewhat

Moderate

Extensive

Previously used

6. Please rank the level of importance each of the following criteria played in your decision to use IDEAL or not *

No importance Slightly important Important Very important Top importance

User baseline knowledge of IDEAL

Support available

Acceptance by REGULATORS

Acceptance by JOURNAL EDITORS

Acceptance by FUNDERS

FINANCE required to complete study

EFFORT required to complete study

TIMEFRAME required to complete study

Validity of IDEAL

7. Did you have any uncertainties about using IDEAL? If yes, please provide details *

Yes No

8. If Yes, what uncertainties did you have about IDEAL?

9. Was advice and support in resolving your uncertainties important for decision in using IDEAL? *

Yes No

10. Do you have any criticisms of the IDEAL Recommendations? *

Yes (please provide details below) No

11. If yes, what criticisms do you have of the IDEAL Recommendations? *

12. Did you use the IDEAL framework in your project? *

Yes No

CORE-MD

ORE-MD, Coordinating Research and Evidence for Medical Devices, aims to translate expert scientific and clinical evidence on study designs for evaluating high-risk medical devices into advice for EU regulators.

For more information, visit: www.core-md.eu

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