Developing a European First-in-Human Study: Three Key Decisions

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A key step in the translational medicine "benchtop to bedside" process model is the move from research and preclinical (*in vivo* or *in vitro*) testing to a "first-in-human" (FIH) study. Despite all efforts to predict how the human body will respond—eg, by conducting robust preclinical testing and risk assessments—there are nevertheless basic anatomical differences between humans and animal subjects that can lead to key differences in performance of a device or therapy.

An essential element of a successful transition from a preclinical to clinical setting is well-managed preclinical studies. Effective preclinical studies that are managed similarly to clinical studies in terms of data collection and completion of case report forms (CRFs) will give greater insight into clinical experience and provide a solid safety profile and risk management plan for the device or therapy. In addition to gaining this critical initial exposure in humans, the purpose of conducting an FIH study is to determine preliminary safety and efficacy of the device and/or the response of the human body to the therapy. Data gathered and analyzed in FIH studies increase the efficiency of the device development process, since these data may lead to modifications to the device, procedure, training, patient selection, and/or clinical study methodology, which in turn will inform future feasibility studies and, eventually, the statistically validated "conformité Européenne" (CE) mark and/or pivotal study.

Many US-based companies choose to conduct FIH studies in EU member countries because the approval process there is fairly straightforward compared to the process and timeline for clinical studies in the US. In planning a European FIH study, there are three critical selections that need to be made by the sponsor company: selecting a European "Authorized Representative" selecting study sites, and selecting a principal investigator ("Investigator").

Selecting an Authorized Representative

As of March 21, 2010, a European Authorized Representative must be designated by a non-EU manufacturer of medical devices who is performing trials in the EU, as required by Directive 2007/47/EC. In order to act as an Authorized Representative, a company must hold an address within the EU and must be registered in their country as a business serving as an Authorized Representative. The company name, address, and identification (Tax ID) are required information for Competent Authority (reviewing body) submission forms, as well as device labels (for devices that are being shipped from outside of the EU to within the EU).

The Authorized Representative, who must be established in the EU, is designated to act on the non-EU sponsor company's behalf with specified responsibilities as per the directive. The Authorized Representative will communicate with the notified bodies in the member states, but the

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manufacturer remains generally responsible for actions carried out by the Authorized Representative. Tasks delegated to the Authorized Representative must be detailed in writing, with attention to the representative's powers and decision-making role.

The Authorized Representative will act as first point of contact with Regulatory authorities and import/customs offices. Per MEDDEV 2.5/10 (A.1.5), "An authorized representative will be addressed by authorities and other bodies in the Community instead of the manufacturer with regard to the latter's obligations under directive [93/42/EEC, 90/385/EEC and/or 98/79/EC]."

Similarly, he/she may need to be present at port of entry to speak on behalf of the manufacturers in support of devices entering the EU. To fulfill the above points, the Authorized Representative will need to develop and maintain a Device Master File and be prepared for audit by EU authorities.

This file will include:

- Declarations of conformity (to EC directives)
- Technical documentation relevant to investigations being conducted
- Manufacturer's Quality Policy
- Incident reports and corrective actions

In reviewing the points of the device master file listed above, benefits can be seen to having the clinical study manager/CRO (in Europe) also act as Authorized Representative. Utilizing an Authorized Representative in a larger management role can provide "on ground" management, including oversight and coordination of all activities. This will help mitigate risks associated with missing required steps in the process of selecting a country and Investigator, obtaining approvals, and executing an FIH study. There is also considerable cross-over in the requirements of the Device Master File to Trial Master File. Similarly, serious adverse events (SAEs) must be promptly reported by the sponsor of the clinical investigation, which could be the manufacturer or the Authorized Representative. In this situation of reporting SAEs, a considerable amount of communication is required between the Authorized Representative and the study manager, especially to adequately address safety concerns in an FIH study. Furthermore, a clinical site audit may be followed (or preceded) by an audit of the Authorized Representative and both the Device Master File and Trial Master File.

Having an effective Authorized Representative to bridge communication among parties—including your Investigator, local ethics committees, and reviewing Competent Authority—is key because he/she is speaking on behalf of the sponsor company. The Authorized Representative must therefore be

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fluent in EU standards, including: MedDev 2.7/4(2012), MedDev 2.7/8(2008), MedDev 2.5/10 (2012), all ISO and ICH standards relating to clinical research, and local governing laws.

While the principal responsibilities of the Authorized Representative are in the development and maintenance of the Device Master File and Trial Master file, and in general communications with the authorities, the decision of who to utilize in this role should not be taken lightly. Choosing an Authorized Representative with appropriate qualifications and expertise is critical. Potential areas of concern include situations in which the Authorized Representative does not understand his/her full responsibility under EU regulations. Care should also be taken to ensure that the Authorized Representative is able and willing to put in the time and money to develop the needed information equipment and database. Finally, as with clinical study managers, the potential of poor relations with the authorities, which may be evident by a lack of apparent transparency of policies and communications, is a concern as that could lead to significant delays in study progress and quality of management.

Selecting Study Sites in Europe

Careful consideration must be given to selecting an optimal country and site to conduct the study. Too often sponsor companies are short-sighted and evaluate only short-term advantages like time to first enrollment or time to approvals. In choosing an EU member state the sponsor should consider several factors that will impact the execution and management of the study.

Directive 2001/20/EC outlines the requirements for conducting clinical trials for EU member states. The Directive provides an outline of the approval and submission process, but each country varies with respect to timing and submission requirements. During the site selection process, representatives from the sponsor company will need to be knowledgeable about the differences in the approval and submission process across the various EU countries in order to understand which country is best suited for conducting the study.

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Unlike the US, there are no central ethics committees or Competent Authorities that can approve studies across countries; therefore, submissions must be made to each country's authorities. Approval in one country may help the submission in another country move along more smoothly, but does not guarantee approval or a more rapid approval time.

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Recently, there has been an increased awareness about the need to harmonize the standards and submission process in the EU member states; however, until harmonized standards are implemented each country's regulations come into play. A sponsor company's Authorized Representative may help evaluate each country's requirement and provide a risk assessment approach with each country. This will help mitigate any delays in submission and approval process up front so company's deliverable and timelines are met.

Despite the EU being a generally desirable location for FIH studies, there remain many variations in the submission process and submission requirements across the EU countries. It may be up to investigator and local ethics committee discretion whether or not Competent Authority approval or notification is required, for example, or whether ethics committee approval alone will suffice. The answer to this question may differ among investigators even within a country. Examples of countries allowing ethics committee approval for single-center studies are the Czech Republic and Slovakia. Many countries will require a favorable opinion from the local ethics committee or multicenter ethics committee first, prior to submitting for approval or notification to the Competent Authority, as in Hungary. In other countries submission to a local ethics committee and Competent Authority may be made in parallel. For multicenter studies conducted in a single member state, a principal site must be chosen and a favorable opinion from the corresponding ethics committee will suffice to submit to the Competent Authority, while obtaining individual ethics committee approval at the other individual centers in parallel or afterwards. In select countries, such as Poland, once approval is obtained from the Competent Authority and the ethics committee from one center, any center in that country is approved and can participate in the study.

Each country will have an essential requirement checklist and forms that need to be completed for the submission. These forms will outline the extent of testing required, such as long-term biocompatibility, sterilization, or unique preclinical testing. Depending on the status of completed testing as well as outcome analyses, a submission may be made without full results with the intent of completion prior to commencing the study. A company should inquire up front about the Competent Authority and ethics committee requirements and should not assume an understanding. The submission documents should be prepared for the benefit of the reviewing parties (Competent Authority and/or ethics committee). The majority of the EU member states will require that trial documents be translated into the local language, including the Clinical

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Investigational Plan synopsis, Informed Consent Form, and documents that are given to subjects. But variations exist here too: in Poland, for example, the full Clinical Investigational Plan is required to be translated.

Another aspect to consider with translation is if a country has two or more local languages, such as Belgium (French, Dutch, and German). The submission documents may need to be translated into multiple national languages. Many countries will also require an executive summary to be translated into the local language(s), as well as any forms required for ethics committee and Competent Authority submission. Thus, having a translator or local Authorized Representative complete these forms is required. Unique to the EU, the Investigator must endorse the submission and study; this is one reason why investigator selection is so important to the outcome of the FIH. On average, once submission is complete to the Competent Authority the review and approval time is 45-90 days, with variations between countries. Ethics committee meetings and review are similar to that of institutional review boards in that they convene on a regular basis and have submission deadlines for each meeting. Ethics committee approval from time of submission is on average 4-6 weeks.

For studies conducted in the EU, each country also requires a unique insurance policy. Unlike US states, a blanket trial insurance policy will not cover all EU member countries. The terms of the policy are typically dictated by the country; however there are varying amounts of coverage a sponsor company may opt for per subject. Eastern European countries typically are less expensive for insurance policies and are thus may be a good option for sponsor companies in this regard. For FIH studies, proper research must be completed on appropriate insurance policies to ensure the sponsor company is fully protected.

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Selecting Investigators

Along with selecting a country, a sponsor company must in parallel consider investigators. Several factors should influence investigator selection in Europe. For FIH studies it is important to select a principal Investigator who is able to provide expert advice and guidance into the design of the clinical study and who also has technical expertise with your product or device. To assess the technical expertise of potential investigators it may be beneficial to have the candidate attend preclinical laboratory or cadaveric study procedures. This may also help mitigate technical issues in the study and will lead to discussions on best practices and techniques that may lessen the risk to subjects and optimize the success of the procedure.

For FIH studies it is critical to plan a study designed to test the device or therapy in an optimal setting and optimal patient population in order to understand the effects in a small sample size. The Investigator should provide input on how to best test a device in his/her patient population to ensure a study design that will not only safeguard subjects but, optimally, will test the therapeutic results of the device in a way that produces meaningful translational data to support a larger pivotal trial design.

It is important to discuss and understand the Investigator's approach to enrolling subjects. Selecting an investigator who is both cautious and aggressive is important to executing an FIH study. A phased or slow approach to enrollment may be beneficial in FIH studies because the Investigator can provide feedback on device functionality and subject response; thus issues are identified in a timely manner. This phased approach will help to safeguard subjects' exposure to unnecessary risks, which would optimally be identified early in the first few subjects. Adequate assessment after each subject enrollment or each subject follow-up/milestone is important in assessing the ongoing risk-benefit analysis of the trial. The Investigator should have open communication with the sponsor and the Authorized Representative throughout the duration of the study to monitor subject response in an effort to adequately identify potential adverse effects and maintain compliance with regulatory reporting requirements.

In essence a sponsor company should look at their Investigator as a long-term partner in that he/she will have initial experience with the product and will provide guidance and expert advice throughout the FIH study, as well as when a larger pivotal trial is launched. Again, an Investigator for FIH studies must be fully engaged in all aspects of the clinical study development, execution, and outcomes.

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Conclusion

Moving from "benchtop to bedside"—beginning with an informative, well-planned FIH study in Europe—is essential to understanding device efficacy and gathering preliminary safety data on its use. Sponsor companies often choose to begin their clinical work in Europe for several reasons, including the desire to engage key physicians in Europe to support future clinical studies for CE Mark certification, to avoid the more arduous regulatory constraints and timelines required to complete the same work in the US, and to benefit from the advantages of being able to complete FIH tests quickly and move into more rigorous research with the feasibility studies, and, ultimately, pivotal studies. To minimize challenges in FIH studies conducted in Europe it is essential to select an effective and resourceful Investigator and Authorized Representative who can provide the level of oversight critical to managing FIH studies. Results from FIH studies could be identified as the most pivotal milestone in a product's lifecycle, and thus taking the time to plan appropriately up front in addressing these challenges and executing the study in the right environment is paramount. Data gathered from the FIH study will drive the next step in the device testing process and will help move the device into a larger feasibility and pivotal trial and continue along the benchtop to bedside process.

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