



# Succeeding in international clinical trials

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Overcoming the challenges of international clinical trials to deliver statistically meaningful results

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## Introduction

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International trials are vital when conducting research into diseases that affect patients worldwide. Over the last two decades, the number of multi-centre trials has been increasing, with one study estimating an increase from 112 multi-centre trials in 1995 to 1,273 in 2010. Over 80% of these were trials conducted in Europe and North America.<sup>1</sup>

One of the aims of multi-centre randomised controlled trials (RCTs) is to ensure that patients get access to new drugs as quickly as possible<sup>2</sup>. But the globalisation of healthcare research brings new challenges, which pharmaceutical companies, central labs and other life sciences companies must work to overcome.

## Key challenges in running international and multi-centre trials

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The top areas which pose challenges when running multi-centre trials can be broadly divided into: statistical, regulatory, ethical, clinical, operational and recruitment challenges<sup>3,4</sup>.

- **Statistical issues** may include the effect that differences between countries will have on the sample size or power estimates for the trial, and differences in randomisation processes.<sup>3</sup>

- **Clinical issues** may include differences in access to healthcare between countries, how diseases are defined and indications for treatment.<sup>3</sup>

- **Operational issues** may include differences in standard operating procedures, access to drugs, training of investigators and the quality of the data obtained from each site.<sup>3</sup>

- **Regulatory issues** may include obtaining approvals from different regulatory bodies and the variation in regulations between different countries.<sup>3</sup>

- **Ethical issues** may include ensuring that full informed consent is obtained from participants, ensuring sufficient safety of the participants, privacy of data, and ensuring the trials follow good clinical practice.<sup>3</sup>

- **Recruitment issues** may include ensuring there are sufficient numbers of participants so that the study has enough statistical power.<sup>4</sup>



Below we have outlined some approaches to resolving a number of the most common challenges, as well as factors to consider when planning a trial, to ensure international clinical trials are fully compliant, efficiently managed and can deliver statistically meaningful results.

## Recruitment

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A study that looked at recruitment for multi-center RCTs funded by the Medical Research Council (MRC) and the UK Health Technology Assessment (HTA) program, found that 55% reached their target sample size between 2002 and 2008, and 30% needed an extension of time.<sup>4</sup> The use of adaptive trials designs, which allow for modifications to be made to the trial design, is one strategy that is increasingly being used to tackle this issue.<sup>4</sup> Additionally, recruiting patients from multiple sites could address the problems with reaching the target power<sup>2</sup> and avoid having to increase the duration of the trial and associated costs.



## Differing regulations

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Each country has their own drug regulatory body with different policies on the use of medicines.<sup>1</sup> Investigators will need to obtain agreements from different health authorities and manage different time frames for review and approval.<sup>3</sup> Several research ethics committees from various countries may be involved in reviewing the trial protocol. Their findings may be conflicting, which could delay the review process and in some cases, approval for the trial could be withheld.<sup>1</sup>

Regulatory authorities in different countries also have different standards. This could be addressed by adapting international standards to the country in which the trial is based. There could also be adaptation of local standards to more closely follow international guidelines.

In the EU there will be a major change to clinical trial regulations in 2018, when the Clinical Trial Regulation EU No. 536/2104 comes into force. This regulation aims to simplify the administrative process for clinical trials throughout the EU.<sup>9</sup> All application documents should be submitted to EU members for approval through a single portal for submissions.<sup>9</sup> EU members have to assess applications within specified deadlines, which is particularly important for trials that involve participants with life-threatening illnesses or where there are very few treatment options for a condition (e.g. very rare diseases).<sup>9</sup>

## Monitoring

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The standards for monitoring trials vary between countries, which can lead to differences in the accuracy and validity of trial data, and the safety mechanisms in place for participants. Multinational study groups need to ensure that there are high standards across all sites even though formal monitoring by regulatory bodies may not be consistent.<sup>1</sup>

## Equipment

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The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) have published guidelines that require sponsors to confirm that facilities and equipment are safe enough to use throughout the trial.<sup>5</sup> This includes documenting certification, accreditation or external quality assessment or quality control.<sup>10</sup>

Many clinical trial sites are chosen because they offer the potential to recruit sufficient numbers of patients, rather than their ability to carry out the trial protocol. As a result, sites may not have the best equipment or expertise to carry out more complex trials. An example of this is where trials involve imaging protocols. If, after a site survey, a trial site is not suitable for the protocol, one option might be to find another facility that does have the required imaging equipment that's near to the trial site.<sup>6</sup>

It's also a challenge to develop a protocol that takes into account the different types of scanner that will be available at different sites, but is specific enough to ensure that each site complies with formal documentary requirements.<sup>11</sup> This could be addressed by writing a basic protocol and then writing separate protocols for each of the manufacturers of the scanners that will be used in the study.<sup>11</sup>

In addition to considering how the chosen trial site may impact equipment requirements at the point of protocol development, an experienced equipment supplier such as MESM can be contracted to manage all elements of equipment supply. This will include ensuring all trial sites receive equipment that is compatible according to the country and regional equipment specifications, and that all end of study reporting requirements are met.



## Importing medicinal products

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The EU Directive 2005/28/EC specifies that a “competent authority” has to give authorisation before medicinal products can be imported into a EU member state.<sup>5</sup> In the US, sponsors of medical devices for use in trials have to be located in the US and the device must be labeled as specified in the FDA regulations.<sup>7</sup>

It is therefore essential that the different requirements for importing medicinal products and medical devices in different countries are taken into account when writing a protocol that includes international trial sites.

## Summary

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Running multisite trials is challenging and requires comprehensive planning, training of staff<sup>13</sup>, and a thorough knowledge of the regulations that apply to the conduct of the trial. Identifying sites that will be committed to the trial process, have the potential to recruit enough participants and can maintain the required standards for quality control are vital to the success of the trial.<sup>8</sup>

*Sites must have the potential to recruit enough participants and be able to maintain the required standards for quality control*

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