Radiopharmaceutical clinical trials – dose is more than sieverts and becquerels

James R. Ballinger • Stephen J. Mather •
Michael J. O'Doherty

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As reviewed recently by Verbruggen et al. [1], clinical trials of radiopharmaceuticals in Europe are regulated by a number of different pieces of legislation in addition to the Clinical Trials Directive. However, it is apparent that European Union member states vary in their implementation of the Directive, some making all guidance mandatory and others interpreting the guidelines reasonably as guidance.

These regulations generally create a lot more work and expense for the clinical researcher. For example, the Clinical Trials Directive requires that an Investigational Medicinal Product Dossier (IMPD) be compiled for any new radiopharmaceutical which is the subject of a clinical trial. The dossier must document a number of aspects of the “drug” component of the radiopharmaceutical, such as its potential toxicity, as well as dosimetry. However, much of this background information is not included in published reports of clinical trials. For example, looking through a number of publications on ^{11}C -choline and ^{18}F -fluorocholine, although the activity administered is dutifully recorded

the amount of drug injected is not normally reported. There is often a source paper which states how the radiopharmaceutical is made and the specific activity of the agent (which would allow calculation of the mass dose), but this does not necessarily apply to the ongoing production of the tracer, particularly if it is adopted in other units duplicating clinical work or using the radiopharmaceutical under different clinical conditions. Furthermore, with short-lived radiotracers the specific activity at the time of administration may be significantly lower than at preparation. The lack of availability of this information is a barrier to further clinical trials and potentially to the rapid dissemination and clinical use of agents, since researchers are unable to quote these data in their own submissions.

We would like to make two proposals to speed up the preparation of an IMPD for clinical trials. Firstly, publications in international journals, including the *European Journal of Nuclear Medicine and Molecular Imaging*, should include as much basic information as possible to facilitate the performance of subsequent trials of the same (or similar) radiopharmaceutical. Specifically, this should include the dose (micrograms or micromoles) or dose range of the agent as well as the activity administered (megabecquerels), an overview of preclinical toxicology, and a description of the monitoring procedures employed and side effects observed in the clinical trial subjects. If necessary, this could be provided as supplementary information to the main article.

Secondly, there should be a freely accessible European central registry of IMPDs, similar to the recording of IND applications in the USA by the National Cancer Institute (NCI). Researchers should be encouraged to file their IMPD and clinical dossiers in this database in order to make the information available to others and thus reduce the workload, time, and costs for subsequent trials. For example, the simplest 14-day toxicity study required for

J. R. Ballinger
Department of Nuclear Medicine, Guy's Hospital,
Guy's and St Thomas' NHS Foundation Trust,
London SE1 9RT, UK

S. J. Mather
Centre for Molecular Oncology and Imaging, Institute of Cancer,
John Vane Science Centre,
Barts and The London School of Medicine,
Charterhouse Square,
London EC1M 6BQ, UK

M. J. O'Doherty (✉)
Clinical PET Imaging Centre, St Thomas' Hospital,
Kings College London and Guys and St Thomas' NHS
Foundation Trust,
London SE1 7EH, UK
e-mail: Michael.odoherty@gstt.nhs.uk

microdosing trials costs in the region of 20–30,000 Euro. Since the development and evaluation of many radiopharmaceuticals is supported by public funds, this seems a reasonable request. Even commercial companies could contribute to such a registry since it is not necessary to release commercially sensitive information. Very few of these agents, particularly those labelled with ^{11}C , have marketing potential. To be most efficient, this database should involve collaboration among the various interested parties including the European Association of Nuclear Medicine (EANM), the European Medicines Agency, the Society of Nuclear Medicine (SNM), and the National Institutes of Health/NCI. The EANM could serve as a central repository for clinical trials information. We would encourage the EANM to conduct a feasibility study among interested parties.

A further extension could be a pan-European multicentre clinical trial network similar to that introduced by SNM whereby a centralized IMPD would be applied for and radiochemistry facilities could then be approved to manufacture following the same process to enable new products

to be studied at multiple centres. We would also encourage EANM to enter into discussions with SNM about combining resources.

The obstacles to the introduction of new radiopharmaceuticals are substantial [2]. Taken together, these proposals will maintain the safety for patients offered by the Clinical Trials Directive, but ease the burden on individual investigators, make better use of the limited noncommercial funding available for clinical trials, and ideally make new radiopharmaceuticals available to patients earlier.

References

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