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EU Trial Review Changes from Reg 536/2014: The Netherlands

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Applied Clinical Trials

Over the past few years, the number of active, accredited Ethics Committees (EC) in the Netherlands has dropped at a steady pace. The decline over the past year has partly been due to the merger of several ECs into one accredited EC (METC Brabant), which now extends its work to research carried out in more than one institution.

The Central Committee on Research Involving Human Subjects (CCMO) expects this trend of EC mergers to continue in response to a call from the field, for ECs to become independent of the institutions they are affiliated with. In current practice, accredited ECs in the Netherlands are independent legal entities but most have a rather substantial financial tie with the institution to which they belong. Therefore, with on-going activities in the Netherlands aimed at reforming hospital finances, more ECs may naturally consider becoming more independent in the future.

There are currently a total of 25 accredited ECs in the Netherlands. The EC at the Academisch Medical Centre (AMC) Amsterdam is the most active (with 260 research protocols reviewed in 2013), followed by University Medical Centre Groningen (UMCG) with 170 reviewed protocols.

Eight of the 25 accredited ECs are linked to an academic hospital, 13 are linked to an institution other than an academic hospital, and four--including the CCMO--are independent.

The CCMO has noticed a rather steep decline in the number of applicants wanting to join the EC board (74) as compared with the previous year (101). The CCMO has also noticed that with the increased complexity and nature of the 'average' trial, for example the use of immunologically active substances on the rise, the accredited ECs may find it more difficult to meet the demand for much needed immunological experts either through retaining them on the EC board or sourcing them as and when needed for clinical trial applications.

The total number of research protocols reviewed by the accredited ECs (including the CCMO) in 2013 was 1,798, which was slightly more than 2012's 1,777 total. Similar to the previous years, slightly more than half (60%) of these were intervention studies, while the remainder were observational studies. Approximately one-third (32%) of the research protocols concerned research with a medicinal product, of which more than half (58%) were sponsored by the pharmaceutical industry. The remaining 42% were investigator-initiated trials.

Table 1 shows the trends in numbers of trial applications in the Netherlands from 2006 through to 2013. There are no clear downward or upward trends in any of the categories, although the total number of trials reviewed in 2010 is slightly below the average, which might be explained by the economic downturn that started in 2008.

Table 1 also shows a consistent trend over the past years, of approximately 40% of all medical trials being IIT, demonstrating there to be a healthy research climate in the Netherlands. This demonstrates that even with the increased stringency of clinical trial regulations, IITs and highly valued academic research in the Netherlands have not been adversely impacted.

In 2013, all custodians of clinical trial applications approved the public use of key data from their application (as entered on the so called ABR form, the compulsory online form in the portal Toetsing Online, used for clinical trial applications to the EC/CCMO). The data from pre-defined data fields on the ABR form are used to feed into the publicly accessible CCMO clinical trials register. The CCMO clinical trials register will display trials after the trial has gained approval, with the exception of Phase I healthy volunteer trials that are posted to the register six months after approval has been granted. The CCMO clinical trial register adds to the transparency for all involved and any person with slightly more knowledge than a layman, could quite easily find particular trials matching an indication of their interest.

UK vs. Dutch ethical review system

Contrary to most of the Dutch accredited ECs, the Research Ethics Committees (RECs) in the UK are independent to an institution. The REC members are entirely voluntary, with only the chairs receiving a small remuneration in recognition of the significant additional responsibilities required of the role. Recently, the UK has also experienced challenges in recruiting REC board members of specific expertise, and consequently has set up a system to co-opt in, which means REC members can be asked to provide their expertise at meetings for other RECs that lack the required expertise.

In the UK, unlike in the Netherlands, which operates in a de-centralized way, clinical trial applicants can make use of verbal and telephone interaction with a central authority, in this case the Health Research Authority (HRA). The HRA will lead and facilitate this interaction, which is aimed at assigning the review of the clinical trial application to the most appropriate REC.

Currently, the HRA is working on a pilot of the effects of offering clinical trial applicants early advice and support. Preliminary findings show that the number of provisional opinions (approvals based on additional conditions to be met by the

applicant) being issued by RECs has fallen and approval timelines have improved.

Effect of EU Clinical Trial Regulation

It is too early to give specifics, but Regulation 536/2014, the new European Clinical Trial Regulation, will have profound consequences for the CCMO to deal with. It is clear that if the Netherlands would like to remain an attractive country for international biomedical research, it needs to change its review system. With its accredited ECs reviewing research protocols in a de-centralized way, the Netherlands clearly have differed from other EU Member States.

Centralizing the ethics review to only one central accredited EC, equipped with a few specialized 'chambers', could be an option. But in this scenario, the research community will lack its current option to be in contact with the often very experienced accredited ECs secretaries, to streamline an upcoming application, and of all stakeholders this might hit the academic researchers the hardest.

It is clear to all that Regulation 536/2014 will be beneficial, predominantly for the multinational clinical trials with medicines. However, this sub-set of research comprises only about 10% of all the research projects that the Dutch accredited ECs deal with. It is therefore a matter for further debate, if managing the rest of the research projects should also change, once the new Regulation comes into effect.

Regarding the part I and part II ethics voting mechanisms in Regulations 536/2014[1], the CCMO has always been of the opinion that science should not be separated from ethics. Therefore, it is and remains opposed to the part I and part II approach, and would like to maintain the system it has in place now, an integrated review. Late in 2013, the CCMO organized several meetings with all Dutch stakeholders. All were of the opinion that (in the future) part I and II should be dealt with by one and the same EC. Also, for the review of national trials, the current system can continue to be used.

For the review of international trials, a new central entity is needed that links in with the EU portal. It is clear that as for all other EU Member States, the Netherlands will soon be changing its review system for clinical trials.

For further information, visit www.ccmo.nl [2]

Table 1.

Table 1. Number of trial applications in The Netherlands - Trends

Year	Total	Of Which (%)					
		Multi-Center	Mono-Center	Medicines			Non-Medicine
					Pharma / Biotech / CRO / Devices / nutr	Other (= IIT)	
2006	1,851	695 (38)	1,156 (62)	627 (34)	Unk	Unk	1,224 (66)
2007	1,827	687 (38)	1,140 (62)	614 (34)	Unk	Unk	1,213 (66)
2008	1,898	705 (37)	1,193 (63)	634 (33)	Unk	Unk	1,264 (67)
2009	1,913	719 (38)	1,194 (62)	628 (33)	Unk	Unk	1,285 (67)
2010	1,707	639 (38)	1,063 (62)	533 (31)	282 (53)	251 (47)	1,169 (69)
2011	1,827	679 (37)	1,148 (63)	584 (30)	323 (59)	225 (41)	1,279 (70)
2012	1,738	668 (38)	1,070 (62)	539 (31)	305 (57)	234 (43)	1,199 (69)
2013	1,798	713 (40)	1085 (60)	571 (32)	333 (58)	238 (42)	1,227 (68)

Rejected trials (non-approvals): 4% in 2011, 2.4% in 2012, 3.4% in 2013

Source: CCMO Annual reports

Reference:

[1]EU Clinical Trials Regulation – part 1: Changes to the clinical trials approvals process. Jo Burmester. http://www.crgcp.org/content/2014/06/27/eu-clinical-trials-regulation-pa... [3] . Accessed July 30, 2014

Sidebar

More on the CCMO

The Central Committee on Research Involving Human Subjects (CCMO) was established on the basis of section 14 of the Medical Research Involving Subjects Act (WMO Law). The CCMO was created in April 1999 and is based in The Hague, the Netherlands.

As the body responsible for implementing the WMO Law, the CCMO has a number of legal tasks, which include:

Oversees the operations of accredited ECs, including approval of appointed EC members, their training requirements and ensuring implementation of adequate quality control measures)

Responsible for keeping track of all clinical trial applications reviewed in the Netherlands since 1999. For any trial application being reviewed by an accredited EC, the CCMO serves as the Competent Authority unless the research is in a special field, such as those pre-defined by the CCMO as being within areas of limited expertise. For these types of research the CCMO serves as the reviewing EC and the Ministry of Health functions as the Competent Authority. The CCMO is also the official appeals body in cases of appeal and objections regarding the accredited EC conduct or accredited EC's final decision on a clinical trial application.

Responsible for publishing its Annual Report. This year's annual report, like those from earlier years, is a particularly good read for all involved in the field of clinical research.

The theme of this year's Annual Report from the CCMO is 'The Future of the Dutch Review System' and for the first time in its history, the report features an interview with an international 'colleague' Mrs. Sue Bourne, PhD, Head of Partnerships & Guidance at the UK's Health Research Authority.

Source URL: http://www.appliedclinicaltrialsonline.com/eu-trial-review-changes-reg-5362014-netherlands

Links:
[1] http://www.appliedclinicaltrialsonline.com/edgar-smeets-phd
[2] http://www.ccmo.nl/
[3] http://www.crgcp.org/content/2014/06/27/eu-clinical-trials-regulation-part-1-changes-clinical-trials-approvals-process/