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The industry needs to think ethical by design. Ethics are difficult to sprinkle on top once a technology has already been developed, they need to be baked in right from the very start

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Denmark has long been a global frontrunner in medical research ethics and now boasts a more robust ethical infrastructure, spearheaded by a new body, The National Centre for Ethics. Head of the Centre's Science and Ethics Division Helle Harder explains the rationale behind its formation, how ethics covers the quality and effectiveness of research beyond just its safety, and how greater interaction with both trial applicants and EU counterparts will ultimately lead to better and more ethical solutions for patients

Can you start by introducing yourself and what brought you to the Danish National Centre for Ethics?

I was trained in human biology and nutritional research, and my career has always focused on clinical research, albeit in different roles. I have been on both sides of the clinical research fence, as both a scientist and investigator within hospitals as well as a trial manager on the industry side during the several years I spent with Novo Nordisk.

Drawing on that experience, I became curious about the role of authorities in influencing the regulatory landscape for clinical research. I therefore moved into becoming a regulatory professional and ended up heading the Danish Medicines Agency’s Department of Pharmacovigilance and Clinical Trials for 13 years.

A year and a half ago I moved on to establish this new organisation under the Ministry of Health in parallel with the national medical research ethics committees that were being created. Today, my full title is head of the Science and Ethics division of the National Centre for Ethics.

What was the rationale behind the establishment of this organisation?

Initially, it was to meet the requirements of the Clinical Trial Regulation (CTR) and implement the decisions and EU guidance into the ethical national system. That was not possible with a decentralised system, creating a need for a central secretariat.

When I started, the secretariat was an area for legal professionals, but we now boast a team with a wider range of professional backgrounds, from researchers to ethicists and philosophers, which enables more qualified assessments across all the committees. We need to better prepare all applicants to ensure predictable outcomes from the committees.

How does Denmark define 'ethics' in terms of medical research, and how does that inform your focus areas at the National Centre for Ethics?

We strengthen our focus on the *quality* of the research in our ethical evaluation. Beyond a 'right or wrong' ethical assessment, we aim to ensure good scientific quality so that patients' exposure to risk is never wasted. If research does not generate new insights or interesting data, it cannot be said to be ethical.

Traditional areas such as informed consent and the recruitment of trial subjects are still key aspects of the evaluation. We remain focused on the traditional ethical themes of minimising harm and ensuring that the potential benefits of the research outweigh the risks. Finally, we have a special focus on vulnerable populations such as people with psychiatric disorders and pregnant women.

A year on from the organisation's formation, what has been achieved and what has the stakeholder reaction been like?

We have been able to build a unique ethical powerhouse in Denmark, covering not only the new medical research ethics committees and the National Health Research Ethical Committees, but also

the general Ethics Council together with the Data Ethical Council. We tap into both planned and emerging synergies of this constellation. This fortified ethical infrastructure is not only welcomed by our stakeholders – it was indeed sought after. Applicants, across the board, enjoy consistently reduced application processing times, increased accessibility, and an increasingly proactive and ambitious ethical authority.

For the pharma industry, the concept of all these ethical committees may seem like somewhat of a bureaucratic roadblock to getting ahead and conducting trials. Can you explain how this 'ethical infrastructure' helps maintain Denmark's attractiveness as a clinical trial location?

We are very eager to actively interact with the industry and the whole ecosystem around clinical research. There is a need to join forces to find good ethical solutions as technologies and methodologies rapidly evolve. The industry needs to think ethical by design. Ethics are difficult to sprinkle on top once a technology has already been developed, they need to be baked in right from the very start.

There is a strong desire on our part to learn which technologies are coming online and how they challenge the regulatory framework, so that we can help industry sponsors to navigate and develop the system better, maintaining good ethics throughout. For this, they need to come to us beforehand so that we can develop solutions together.

It is extremely important that companies get good advice, meaning that we should be easily accessible and provide a qualified sounding board to discuss their challenges. It is also clear that industrial research is very important for society, as is the quality of hospital treatments and experimental research. For this reason, we try to meet short timelines. Our 2022 performance numbers are fresh off the press and are really impressive. 96 percent of applications under the directive are handled within the 60-day timelines. Mean decision times are close to half of the timelines of 60 and 45 days for pharmaceutical and medtech respectively.

Good European guidelines are crucial for uniform regulatory interaction across the EU. The ethical system and the European systems have historically been almost like strangers, but because of the CTR we have been invited into the EU processes. We now need to get up to speed in the ethical system to harvest all this potential, have predictable demands for sponsors, and create EU-wide ethical guidelines as already exist for national-level regulatory bodies.

Given Denmark's advancement in the ethical field, do you see the Danish National Centre for Ethics as having a leading role to play in this EU-wide ethical shift?

There is a huge potential for ethical EU alignment to create better predictability. Currently, there is no infrastructure that can facilitate the discussion of an ethical regulatory framework. We are therefore proposing a European body that can act as a platform for the national ethical bodies. With this, we would be able to discuss the ethical challenges with new technologies and methodologies across Europe. We know that this is very much welcomed by our industry stakeholders: we recently gathered the entire Danish clinical trial ecosystem to share experiences and expectations from the first year with the European Clinical Trial Regulation. Among the participants were international commercial trial sponsors. These participants expressed concern that the administration of the new EU regulation may not adhere to the legislative intent of alignment. The commercial sponsors, in particular applauded the idea of increased EU-wide alignment of ethical evaluation.

Do you sense a growing level of receptiveness from your colleagues on an EU level to the ideas that you are bringing forward? Are these concerns seen more as 'nice to haves' rather than 'must haves' in more resource-constrained contexts?

Things are maturing, but it takes time. The ethical system needs to see what it is facing in the EU and what the demands are, because it's been a black box that has not previously been part of the EU system.

Among my colleagues in the EU, the idea of speaking across countries and creating guidance is definitely maturing. For example, we created the first national ethical decentralised clinical trial (DCT) guidance, which was then taken to the EU level and contributed to the recently issued EU-level guidance. This is probably the first time that the ethics system has actively contributed to EU guidance.

Beyond Europe, do you have any interactions with colleagues in the US or developing countries, or is this something for further down the line?

Not yet. However, when I was at the Danish Medicines Agency, I was in contact with the South Korean regulator and the US FDA among others, all of whom were very interested in how Denmark was going to organise its ethical system with a centralized secretariat.

From an ethical perspective, what are some of the key concerns to bear in mind around the emerging theme of decentralised clinical trials?

We welcome the increased use of decentralised elements in clinical research. Participants tell us that they like the flexibility and how they decrease the participation burden. For a sick person, spending time and energy going back and forth from a trial site is exhausting. Additionally, DCTs can broaden the trial participation base, including those from a wider geographic region, or those with jobs that would make it otherwise impossible to attend. Additionally, the continuous data collection that a decentralised design more often utilise, can create a much more granular and credible basis for evidence.

From an ethical point of view, ensuring patient safety when procedures may be being performed by the patient themselves or by an external contractor rather than by a doctor in a hospital is a key concern. In this decentralised setting, patient monitoring changes, as does the informed consent and data collection process.

Denmark has always been strong on patient data collection, but how does this play into the ethics question?

We believe that decisions throughout the healthcare system should be driven by data. In terms of DCTs, for example, there is a lot of hype around generating a large amount of data from wearables. However, we must bear in mind that it is not ethical just to collect a lot of data. Data collection should always be for a purpose. There should be validated endpoints, an idea of where the data should be used, and how it will positively impact patients.

There is currently a lot of industry hype around the potential impact of ‘clinical trial diversity’. How do you see this trend from an ethical perspective?

Diversity is, of course, important and something we welcome. There has historically been a lack of women in clinical research, for example. Nevertheless, in this diversity push, the industry must not

forget representability. It is vital that they ensure that the study population is representative of the population that the research is intended to benefit.

What are your goals for the next few years?

We want to build on our existing work at the frontier of ethics in medical research, including the creation of the ethical research committee system. This has existed for over 40 years, but the CTR gives us a golden opportunity to rethink, remodel, and modernise the system to adapt to new technologies and methodologies on both a national and EU level.

We must continue to interact with the whole ecosystem to pick up on new trends and identify challenges earlier. This includes greater levels of interaction with trial applicants, as well as with our colleagues across Europe. The future is one of mutual feedback where we learn from applicants, as well as educate them, and design strong ethical solutions together.

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