



Workshop On Refining The Regulatory Context Of Controlled Human Infection Models

Framework for ethical review from CCMO perspective

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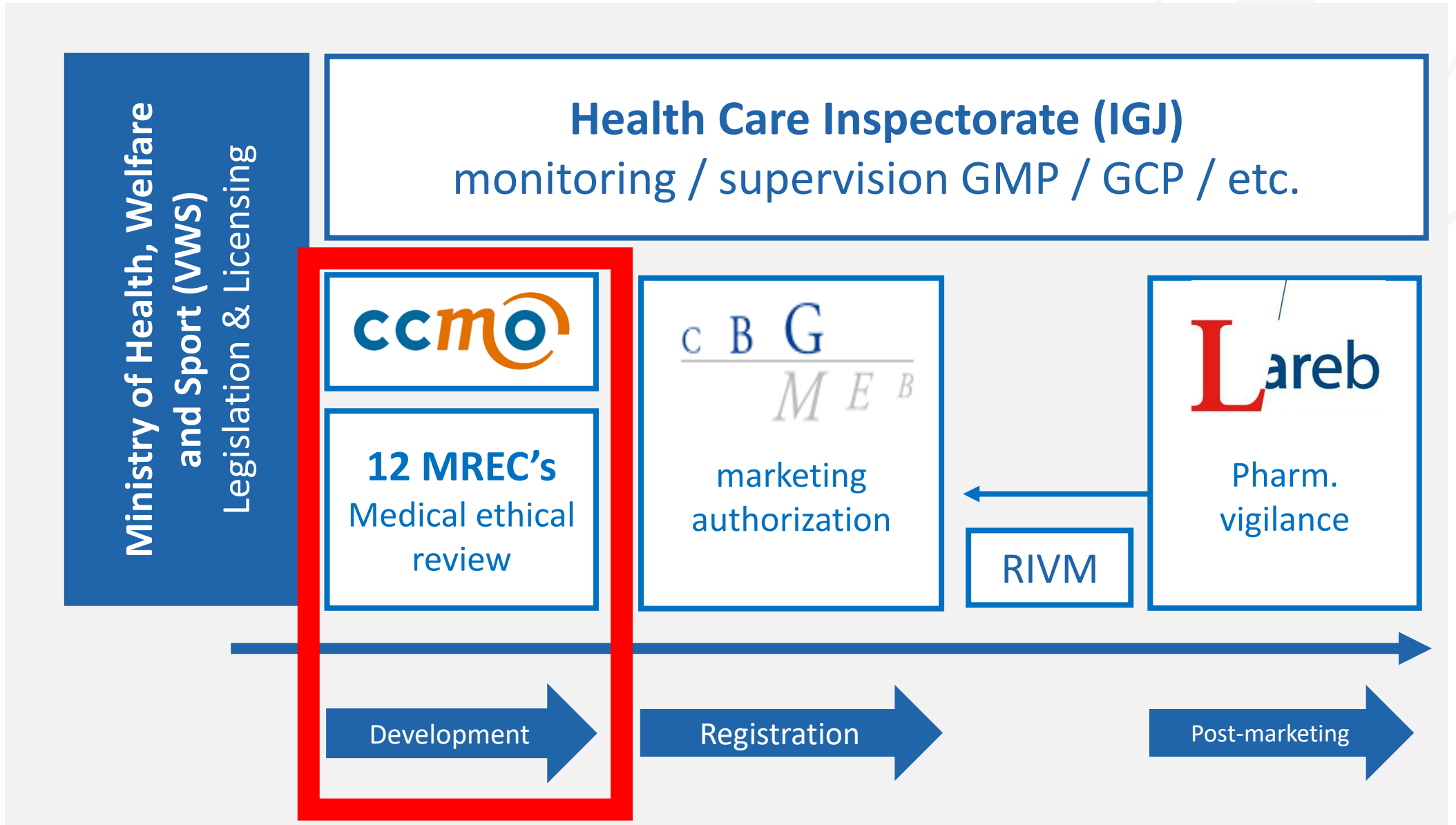
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Medical-ethical review of clinical research in the Netherlands



The Dutch Medicine Chain



The Dutch

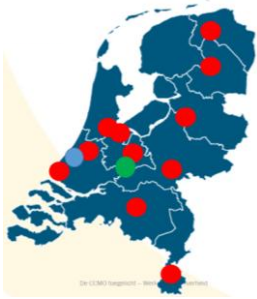


● 12 Medical Research & Ethical Committees (MRECs)

● **ccmo**

● $\frac{c \ B \ G}{M \ E \ B}$

Two competent authorities:
CCMO + MRECs → clinical trials
MEB → Medicinal products



The Dutch reviewing system

Medical Research and Ethical Committee

Each committee has more than 30 members

Defined disciplines:

- Physicians
- Methodologists
- Ethicists
- Lawyers
- Paediatricians
- Pharmacists
- Pharmacologists
- MDR experts
- Patient and Research participant representatives



Central Committee on Research Involving Human Subjects

Review committee

Overseeing the accredited medical research ethics committees (MRECs)

Administrative body of appeal

Coordination of CTR studies in case NL is in the lead

Review of research with specific ethical, legal or social aspects and research in fields with limited expertise



Central Committee on Research Involving Human Subjects

Examples of research reviewed by the CCMO

Non-therapeutic interventional research with subjects <16 years of age and incapacitated subjects


Research on

Unauthorised prophylactic **vaccines, cell therapy, gene therapy**

Research with

Products containing **living (micro-)organisms or viruses**

Human gametes, embryo's, fetuses



Developing ethical guidance for research ethics committees in the Netherlands to evaluate the use of controlled human infection models

Rationale of this project

- Protocols with controlled human infection models (CHIMs) often lead to extra ethical and legal questions, including among research ethics committees (RECs).
 - E.g., risks for the participant and third parties, classifying challenge pathogens, selection of participants, and what appropriate reimbursement would be.
- Simultaneously, some have raised the question whether it would be ethical to not use a CHIM for the development for vaccines (Savulescu 2020; Eyal et al. 2021; WHO 2021).
- There is increased demand for an adequate and useful ethical framework for RECs.
 - The number of CHIMs has strongly increased on a global and national level (Diavatopoulos & De Graaf 2023; Adams-Phipps et al. 2023)
 - The COVID-pandemic has shown that a successful pandemic CHIM requires a clear, widely shared ethical framework (Jamrozik & Selgelid 2020; Sha et al. 2020; Weijer 2024; Dawson et al. 2020).

This project

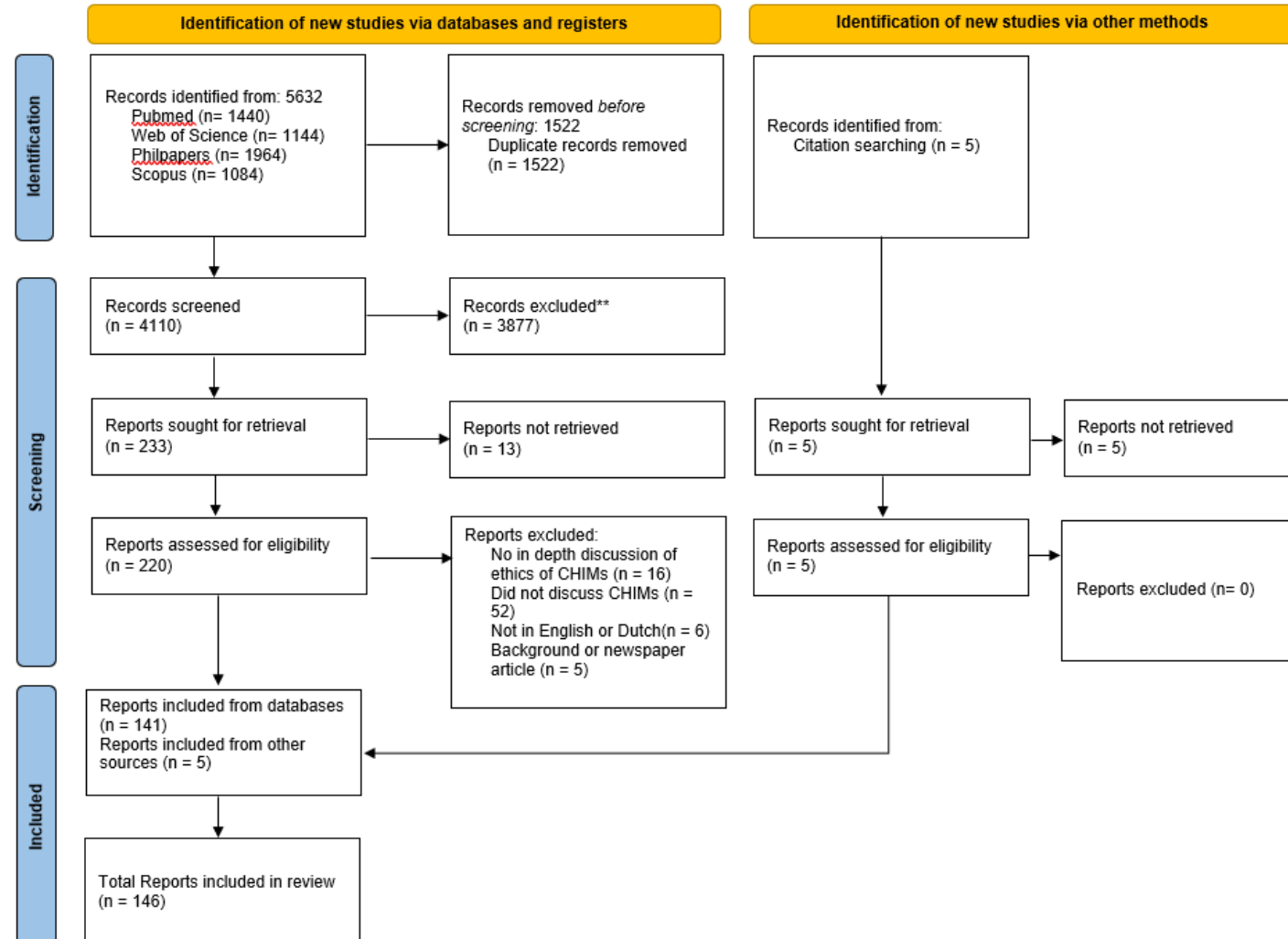
- WHO is working on harmonizing existing ethical principles, but contextualization of these principles for the Dutch practice is necessary.
- According to which criteria should RECs in the Netherlands evaluate the use of CHIMs?

CCMO commissioned project with three phases:

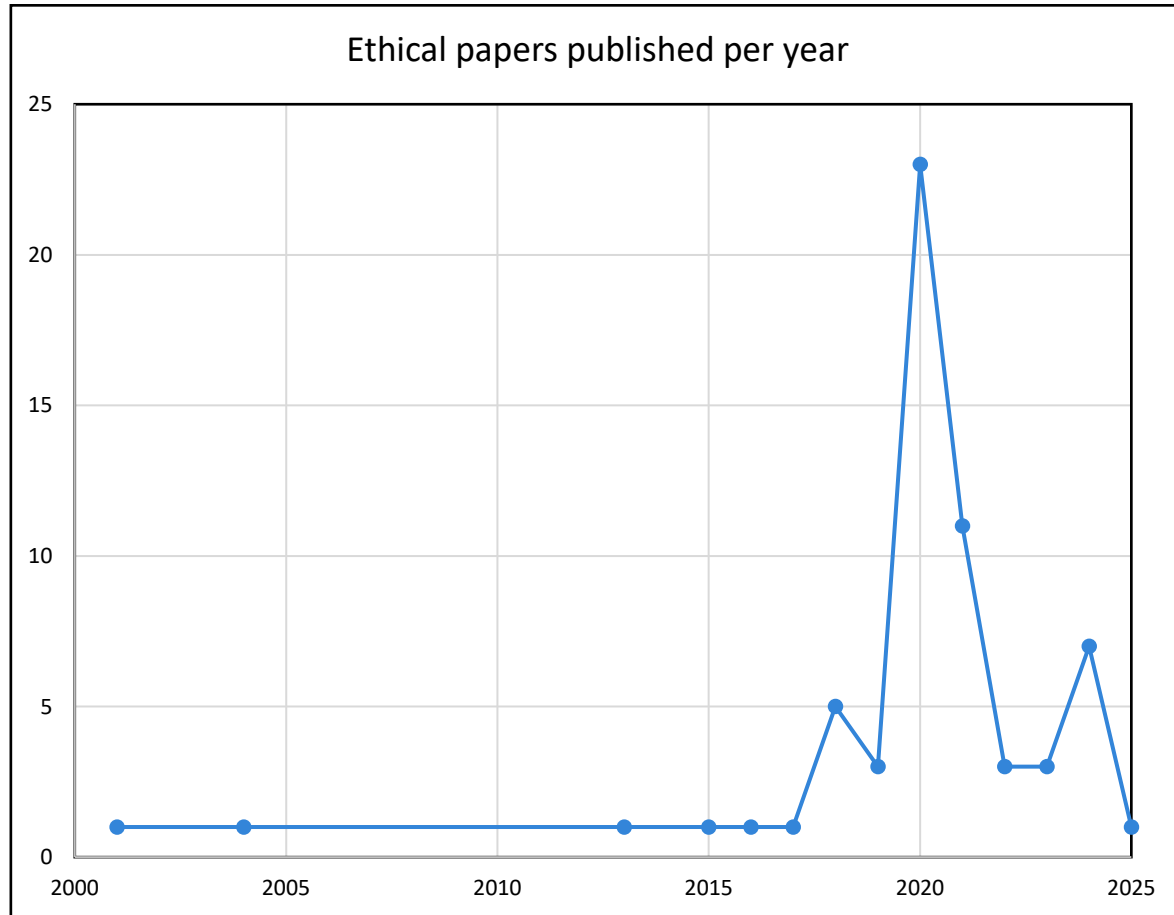
1. Systematic review of the literature and RECs documents
 2. Focus group studies with stakeholders
 3. Development of an ethical framework for Dutch RECs
- Today we will present preliminary results of phase 1

Systematic review

- Databases: Pubmed, Web of Science, Philpapers, and Scopus
- Search strategy included search terms like "Human Challenge Trials as Topic", "Human Challenge*", "Controlled Human Infection*", CHIM*, "Controlled Infect*", in combination with "Research Ethics", Ethic*, Bioethic*
- 5632 reports found, 146 reports included after screening



Results



Type of paper	n	%
Ethical arguments	62	42%
Qualitative research	24	16%
Commentaries/response/editorial	20	14%
Meeting reports	17	12%
Reviews	15	10%
Other	8	5%
Total	146	

Ethical arguments		
Pathogen	n	%
Covid	32	52%
No specific focus	22	35%
Malaria	4	6%
Dengue	2	3%
Hepatitis C	2	3%
Zika	2	3%
Tuberculosis	1	2%
Setting	n	%
Pandemic	32	52%
Not specified	20	32%
Endemic	10	16%
Epidemic	1	2%

Ethical themes

Ethical topics discussed	n	%
Risks to participants	49	79%
Social & scientific value	38	63%
Participant selection	32	53%
Informed consent	29	48%
Public engagement	22	37%
Third party risks	21	35%
Necessity	20	33%
Payment to participants (general)	17	28%
Maintaining public trust	16	27%
Trial site selection	16	27%
Other	8	13%

Ethical topics discussed	n	%
Compensation for adverse events	8	13%
Independent/extra ethics review	8	13%
Transparency	6	10%
Ethics review	4	7%
Collaboration between researchers	4	7%
Challenge model approval	3	5%
Right to withdraw	3	5%
Building a research infrastructure	4	7%
Rescue therapy	2	3%
Use of scarce resources	2	3%
Concerns about exploitation	1	2%

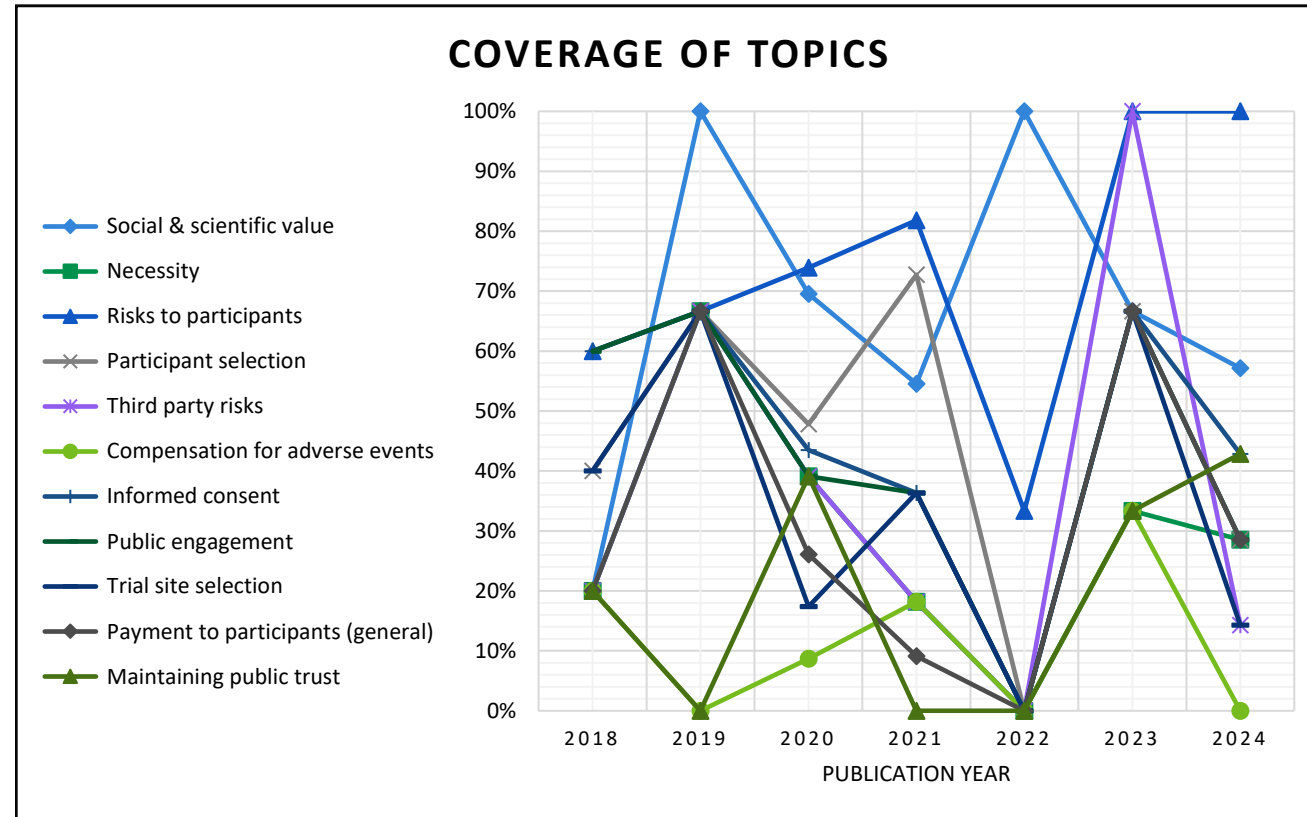
Topics per pathogen

Ethical topics discussed	No specific pathogen		Covid		Malaria		Dengue		Hepatitis c		Zika		TBC	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Risks to participants	16	73%	27	90%	3	75%	1	50%	2	100%	0	0%	1	100%
Informed consent	11	50%	12	40%	3	75%	1	50%	1	50%	1	50%	1	100%
Participant selection	10	45%	17	57%	2	50%	0	0%	2	100%	1	50%	1	100%
Third party risks	9	41%	5	17%	2	50%	1	50%	2	100%	2	100%	1	100%
Maintaining public trust	9	41%	6	20%	0	0%	0	0%	0	0%	1	50%	1	100%
Social & scientific value	8	36%	22	69%	3	75%	2	100%	2	100%	2	100%	1	100%
Necessity	8	36%	8	27%	1	25%	1	50%	2	100%	1	50%	0	0%
Public engagement	7	32%	9	30%	1	25%	1	50%	1	50%	2	100%	1	100%
Payment to participants (general)	7	32%	5	17%	2	50%	1	50%	1	50%	1	50%	1	100%
Compensation for adverse events	4	18%	3	10%	1	25%	0	0%	1	50%	0	0%	0	0%
Trial site selection	4	18%	8	27%	1	25%	1	50%	1	50%	1	50%	1	100%

Topics for different settings

Setting	Not specified		Endemic		Pandemic	
	n	%	n	%	n	%
Ethical topics discussed						
Risks to participants	15	75%	8	80%	27	84%
Informed consent	11	55%	6	60%	12	38%
Maintaining public trust	9	45%	2	20%	6	19%
Participant selection	8	40%	6	60%	17	53%
Third party risks	8	40%	7	70%	5	16%
Social & scientific value	6	30%	9	90%	22	69%
Public engagement	6	30%	6	60%	9	28%
Necessity	5	25%	6	60%	8	25%
Payment to participants (general)	5	25%	6	60%	5	16%
Compensation for adverse events	3	15%	2	20%	3	9%
Right to withdraw	3	15%	0	0%	0	0%
Trial site selection	2	10%	5	50%	8	25%
Other	2	10%	1	10%	4	13%
Ethics review	1	5%	3	30%	0	0%
Challenge model approval	0	0%	1	10%	2	6%
Transparency	0	0%	4	40%	2	6%
Independent/extra ethics review	0	0%	3	30%	5	16%
Collaboration between researchers	0	0%	1	10%	3	9%
Building a research infrastructure	0	0%	4	40%	0	0%

Ethical topics per year



Questions from RECs

- Letters sent from the RECs (local and national) to the researchers.
- 17 letters from 10 studies
- 3 malaria, 3 hookworm, and others
- What kind of topics did they address in their questions to researchers?

Topic	Files	References
Methodological questions	15	56
Disclosure and informed consent	14	113
<i>Clarifying PILs</i>	13	105
Risks and burdens participants	14	55
<i>Potential benefits</i>	1	1
<i>Unexpected findings</i>	2	3
<i>Risks and risk minimization</i>	11	36
<i>Time and other burdens</i>	7	10
Small corrections	12	51
Product information	11	26
Storage and use of personal data and biological samples	10	32
Other administrative and legal questions	8	12
Compensation and reimbursements	8	23
<i>General reimbursement</i>	5	12
<i>Insurance</i>	5	11
Risks for third parties	4	5
Social value CHIM	4	6
Withdraw participant	3	5
Necessity CHIM	2	3
Finance	1	1
Independence physician	1	1
Selection study location	1	1

Methodological questions

While these questions are often about clarifications of the protocol, sample size, or outcomes, they can overlap with other ethical questions, such as risks or social value.

“Given the side effects of [drug], the committee requested an explanation of why participants exposed only to [control] are also treated with [drug]. [...] The [REC] recommends either using a placebo for [control], which is unpleasant or bitter but differs from [drug] in terms of shape and taste, or not administering a placebo for [control].”

	Files	References
Methodological questions	15	56
<i>Clarifying protocol</i>	9	26
<i>Sample size</i>	7	9
<i>Outcome and evaluation</i>	4	7
<i>Necessity certain procedures</i>	2	2
<i>Other questions</i>	8	12

Risks and risk minimization

Main risks discussed: risk of the pathogen, selection of participants, and medication and side-effects.

“Before new clinical trials are initiated, the cause of the adverse events [x] and a plan to prevent them (e.g., a different strain) should be further investigated.”

“Why are women of childbearing age also included? (If the test subject does become pregnant within three years, there are potential risks to the fetus?)
Couldn't male donors suffice?”

Topic	Files	References
Risks and risk minimization	11	36
<i>Medication and side-effects</i>	5	8
<i>Monitoring</i>	2	3
<i>Risks of the pathogen</i>	9	13
<i>Selection of participants</i>	5	9
<i>Stop rule</i>	3	3

Correspondence with the RECs

Which questions would you expect from a research ethics committee based on the specific pathogen you are researching?

- Are there ethical questions that you find unclear or difficult to answer?
- Do you feel that some ethical topics are overlooked or overemphasized in the ethical evaluation of your protocols?

The role of the CCMO

Should the CCMO or other RECs be involved in the development of IMPD before submission?

- Should the CCMO (also) have a role in the later development pathway at the Dutch MEB or the EMA?

Streamlining ethics review

Should protocols for CHIMs (or other documents send to the REC) standardly include a checklist for ethical issues to identify and resolve ethical issues early on?

- Example: checklist bystander risk of Lammers and colleagues (forthcoming)

Risk to bystanders/risk of transmission

How infectious is the pathogen under study?

Is there a risk of transmission for bystanders?

What are the chances of transmission, should the infectious agent be released in the environment?

Are there susceptible members of the population that need to be protected from the disease under study?

What steps can be taken to protect these susceptible populations from infection?

What is the background risk of infection for this particular disease in the general population?

What measures need to be put in place in general to avoid transmission?

Are quarantine measures for participants necessary and if yes, how long and how much will quarantine measures affect participants?

Is the informed consent and participant information clear about which measures (e.g. quarantine) are put in place to protect bystanders and how this will affect participants' ability to retire from the study at any time?

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