NATIONAL OFFICE FOR RESEARCH ETHICS COMMITTEES

Insights into Committee business

Dr Susan Quinn, Programme Manager for NREC-CT

Dr Lucia Prihodova, Programme Manager for NREC-MD

National Office webinar 27/10/2022

Agenda

- NREC-CT
- NREC-MD
- Spotlight on key topics
- Q&A

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NREC-CT

Committees, remit and work to date

Is my study a CTIMP?

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The remit of the NREC-CTs is to review the submission of ethics applications related to Clinical Trials of Investigational Medicinal Products (CTIMP).

This includes interventional studies and low-interventional studies involving medicinal products for human use.

https://health.ec.europa.eu/system/files/2016-11/ctqa_v11_0.pdf

NREC-CT Structure

	NREC-CT A B
Scope	**Clinical Trials of Investigational Medicinal Products SI190 (CTD) & CTR**
Membership	23 each for A & B
Meeting frequency	Two main meetings per month, two subcommittee meetings per month
Reporting	Minister for Health
Operational support	National Office
Remit	New clinical trial applications, substantial amendments, safety notifications, corrective measures

https://www.nrecoffice.ie/committees/nrec-ct/nrec-ct-a-members/
https://www.nrecoffice.ie/committees/nrec-ct/nrec-ct-b-members/

Volume to date: NREC CT

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Year	New applications		Substantial amendments		Total		
	Received & deemed invalid	Reviewed by NREC-CT	Received & deemed invalid	Reviewed by NREC-CT	Received & deemed invalid	Reviewed by NREC-CT	**Total**
2021	15	49	24	216	**39**	**265**	304
2022	19	50	44	332	**63**	**382**	445
Total	**34**	**99**	**68**	**548**	**102**	**647**	**749**

Time to decision: approx. 39 days

Volume of CT Applications to date

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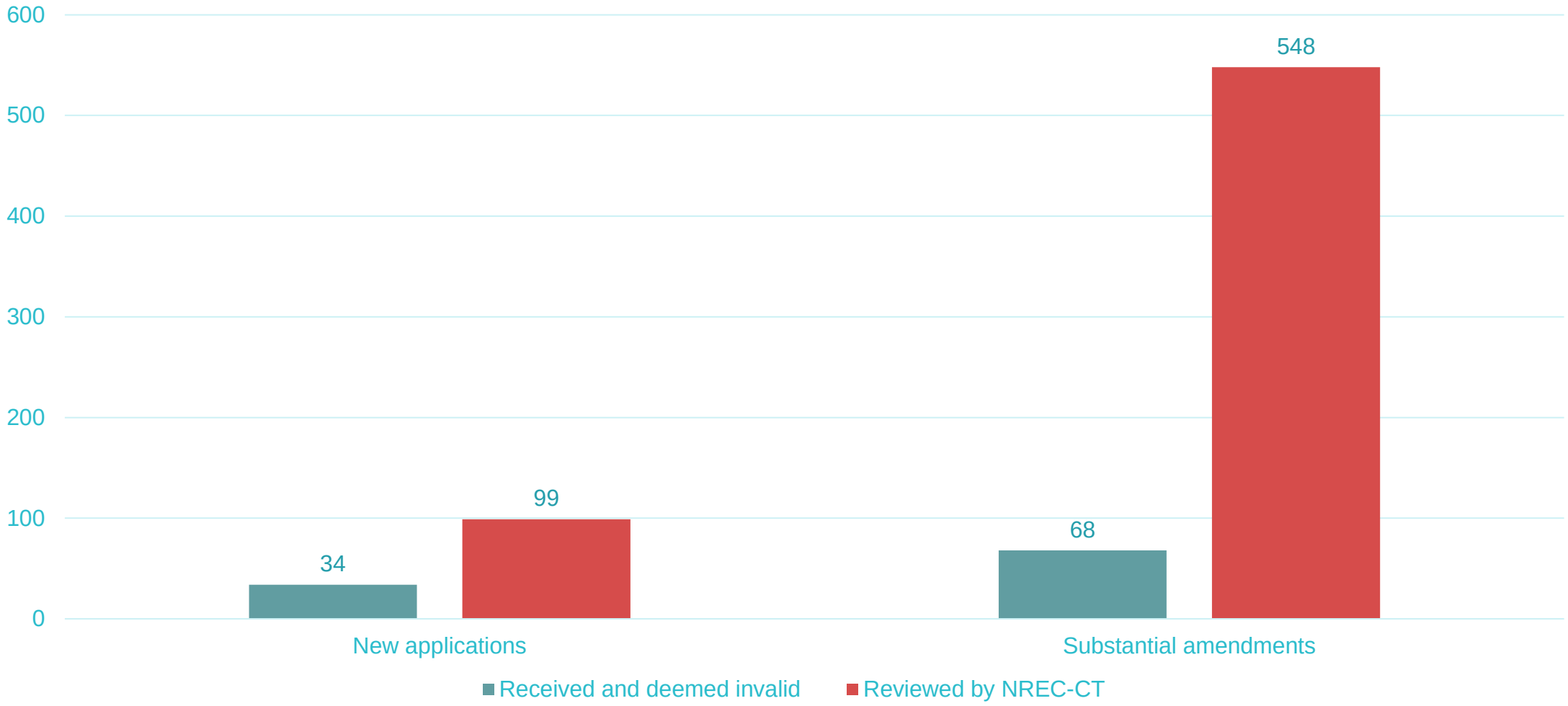

Substantial Amendments: volume and bootcamp

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Substantial amendments

		Decisions made		
	# Amendments considered	Request for further information	Favourable	Favourable with conditions
Week 1	20	1	13	6
Week 2	20	4	14	2
Week 3	20	5	9	6
Week 4	20	9	2	9
Week 5	20	8	9	3
Week 6	15	3	4	8
Week 7	12	0	7	5
Week 8	7	3	4	
Total	**134**	**33**	**62**	**39**

- SA submissions greatly exceeded volume forecast – resulted in backlog in early 2022
- National Office & NREC with support of Dept of Health devised a solution
- 8 week Bootcamp
  - 14 members from CT-A/B came forward to help tackle the task
  - 134 Substantial Amendment applications reviewed over 8 weeks
  - Decision breakdown:
    - 33 RFI
    - 39 Favourable with conditions
    - 62 Favourable
- Future steady state
  - 10 additional NREC members
  - 2 Subcommittees per month
  - Monitoring
  - Current average time from validation to decision: 25 days

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NREC-CT

CTD & CTR: upcoming changes

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Why is the new Clinical Trial Regulation important for Ireland?

It fosters innovation across borders and encourages the development of new treatments for patients in Ireland and across Europe.

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What does the new Clinical Trial Regulation mean for Irish patients and the public?

It means greater transparency in and access to clinical research conducted in Ireland and across Europe.

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What does the new Clinical Trial Regulation mean for Irish researchers?

It creates a harmonised system for the assessment of clinical trials in Ireland and across Europe.

Clinical Trials Regulation (CTR)

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- 31st January 2022, currently within the 12-month transition period
  - Applications and assessments are managed through a new, unified online portal known as the Clinical Trial Information System (CTIS)
  - The authorisation procedure is split into two stages:
    - Part I: a coordinated scientific assessment of the application: HPRA & NREC
    - Part II: an ethical assessment carried out by NREC. Country-specific and site-specific documents by each member State according to its own national requirements
  - Following this procedure, each Member State will reach its own outcome

HPRA Presentation: Transition trials
HPRA Presentation: Substantial Amendments
NREC Presentation: Preparation for the CTR

Clinical Trial Regulation
Timeline

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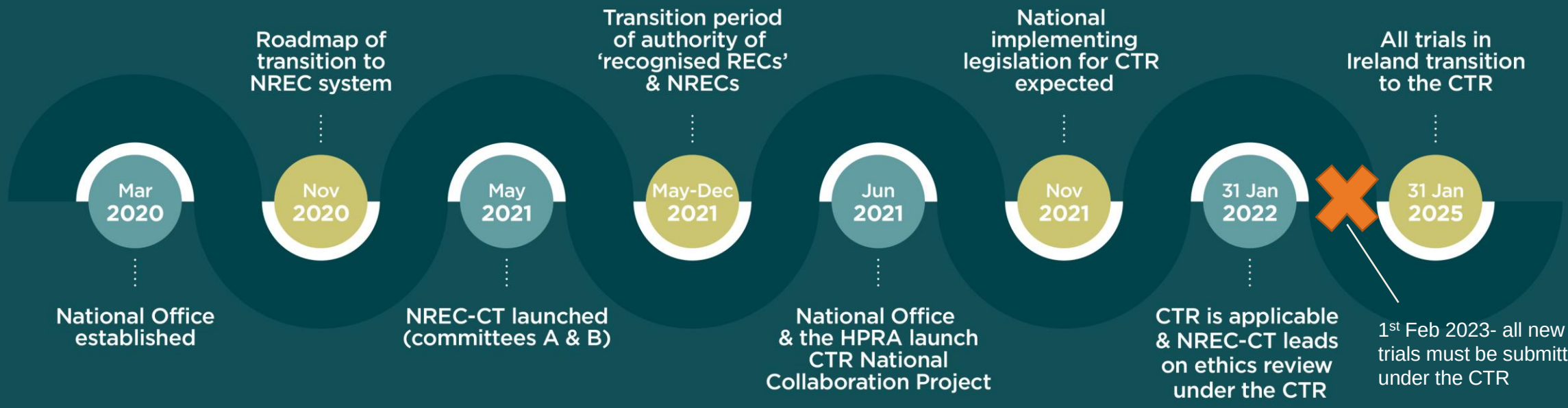
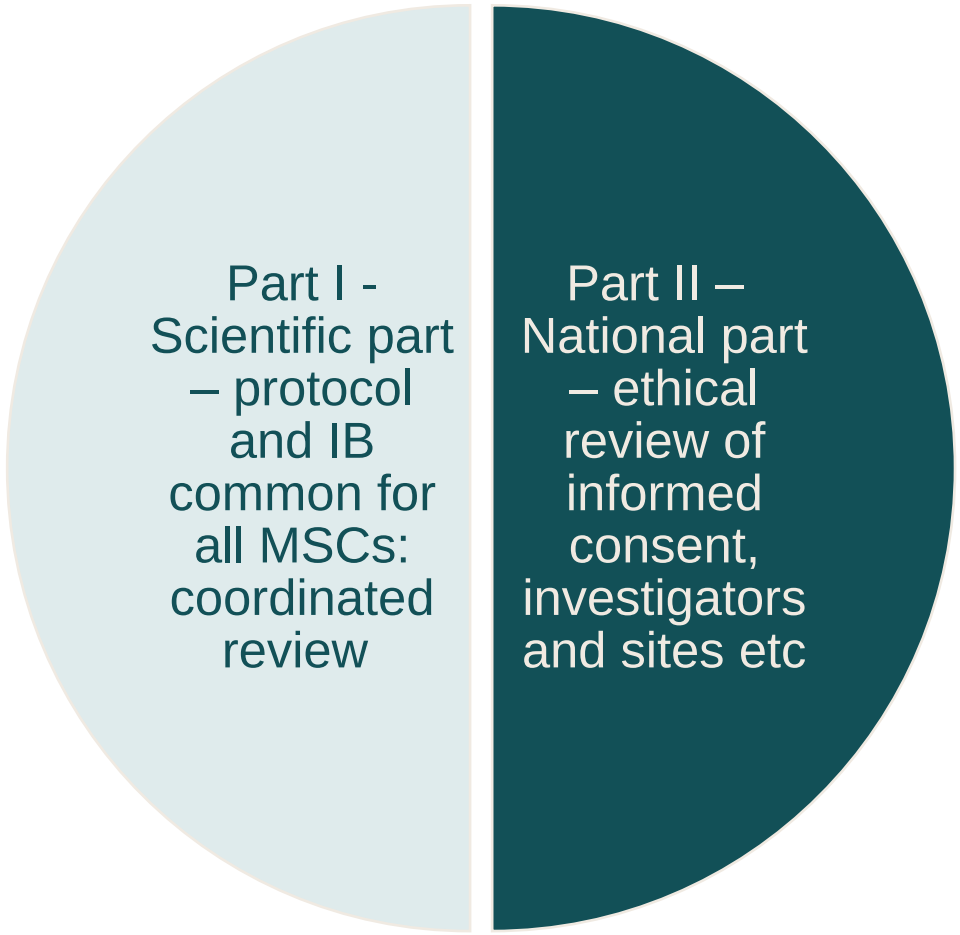


CTR Clinical Trial Regulation
HPRA Health Products Regulatory Authority
NREC(s) National Research Ethics Committee(s)
NREC-CT National Research Ethics Committee for Clinical Trials of Investigational Medicinal Products
REC(s) Research Ethics Committee(s)

nrecoffice.ie

Changes for the NREC-CT



- Part I and Part II do not need to be submitted together:
  - NREC-CT may be reviewing Part I and Part II separately – potentially 2 years apart
  - No requirement for an applicant to submit a Part II
- NREC-CT will only have one opportunity to request changes or further information under an RFI for both Part I and Part II
- Conditions as part of a ‘Favourable’ decision are restricted to those that that cannot be fulfilled at the time of authorisation
- Applicant can appeal an NREC-CT decision

Major change for ethics review

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Opportunities

- Harmonised submission: single entry point, documents, fee, national decision
- Fostering collaboration
- Improved transparency
- Major benefits to Irish patients

Uncertainties

- Volume of submissions
- Delayed Part II submissions
- Strict deadlines
- Multinational coordination
- Reliance on volunteer systems

CTD – CTR Transition 2023

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NREC	SUBMISSION CUT OFF DATES 2022/2023	MEETING DATE
NREC CT B	10 November 2022	23 November 2022
NREC CT A	24 November 2022	7 December 2022
NREC CT B	*Break*	*Break*
NREC-CT B	15 December 2022	11 January 2023
NREC-CT A	11 January 2023	25 January 2023
NREC-CT B	**25 January 2023 (last date for submission of valid new applications under the CTD*)**	8 February 2023
NREC-CT A	**8 February 2023 (all submissions must be through the CTIS system under the CTR)**	22 February 2023
NREC-CT B	1 March 2023	15 March 2023
NREC-CT A	15 March 2023	29 March 2023

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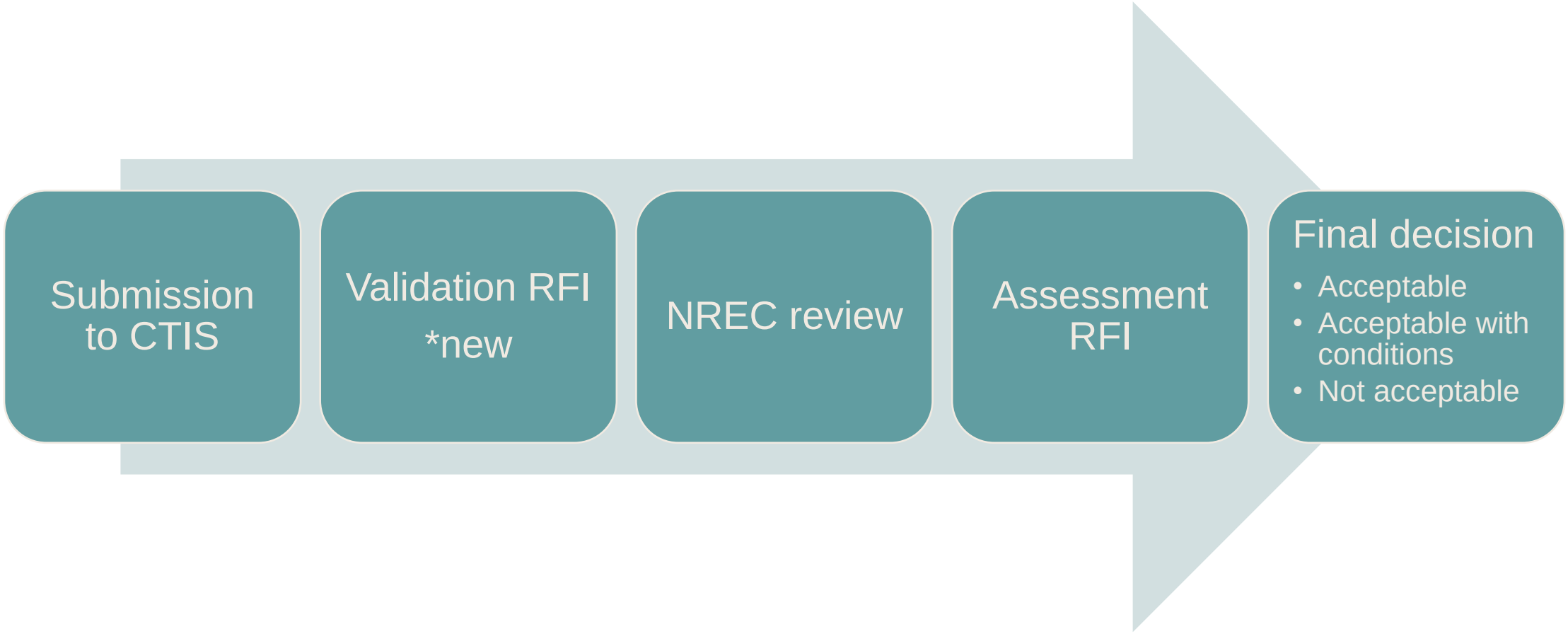
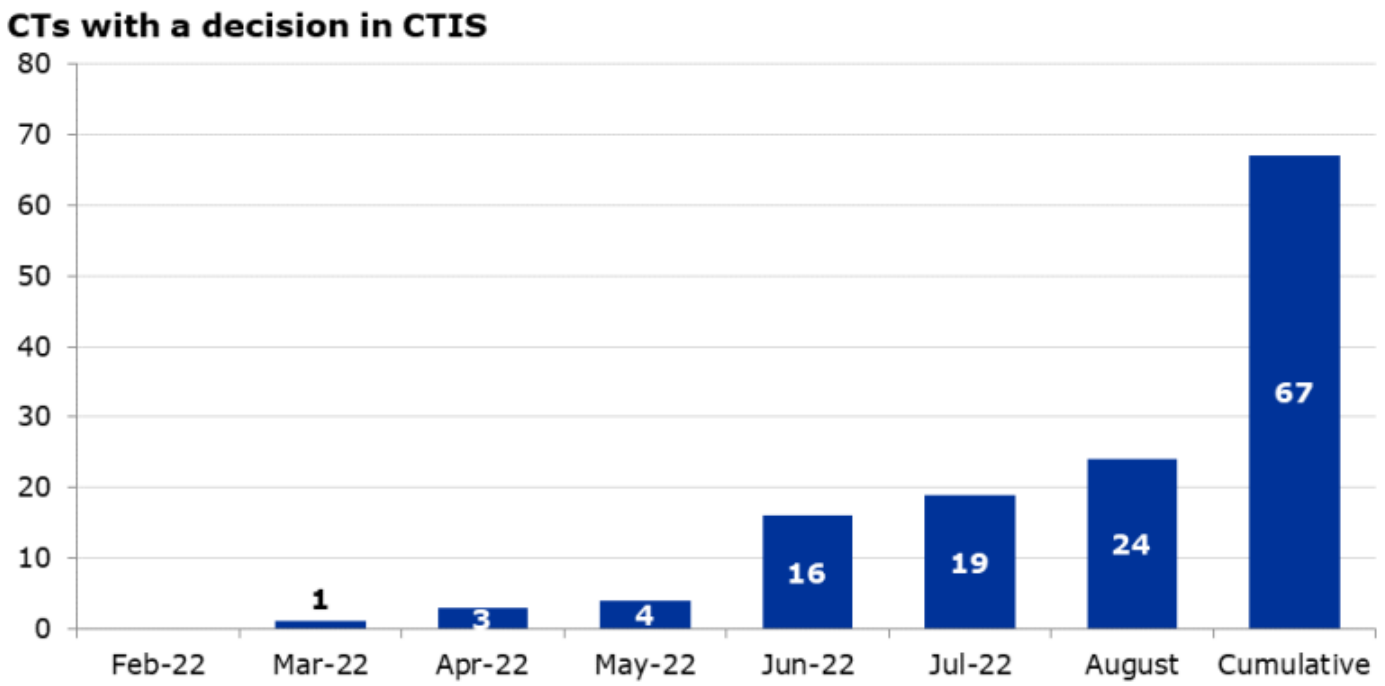
CTIS Review process

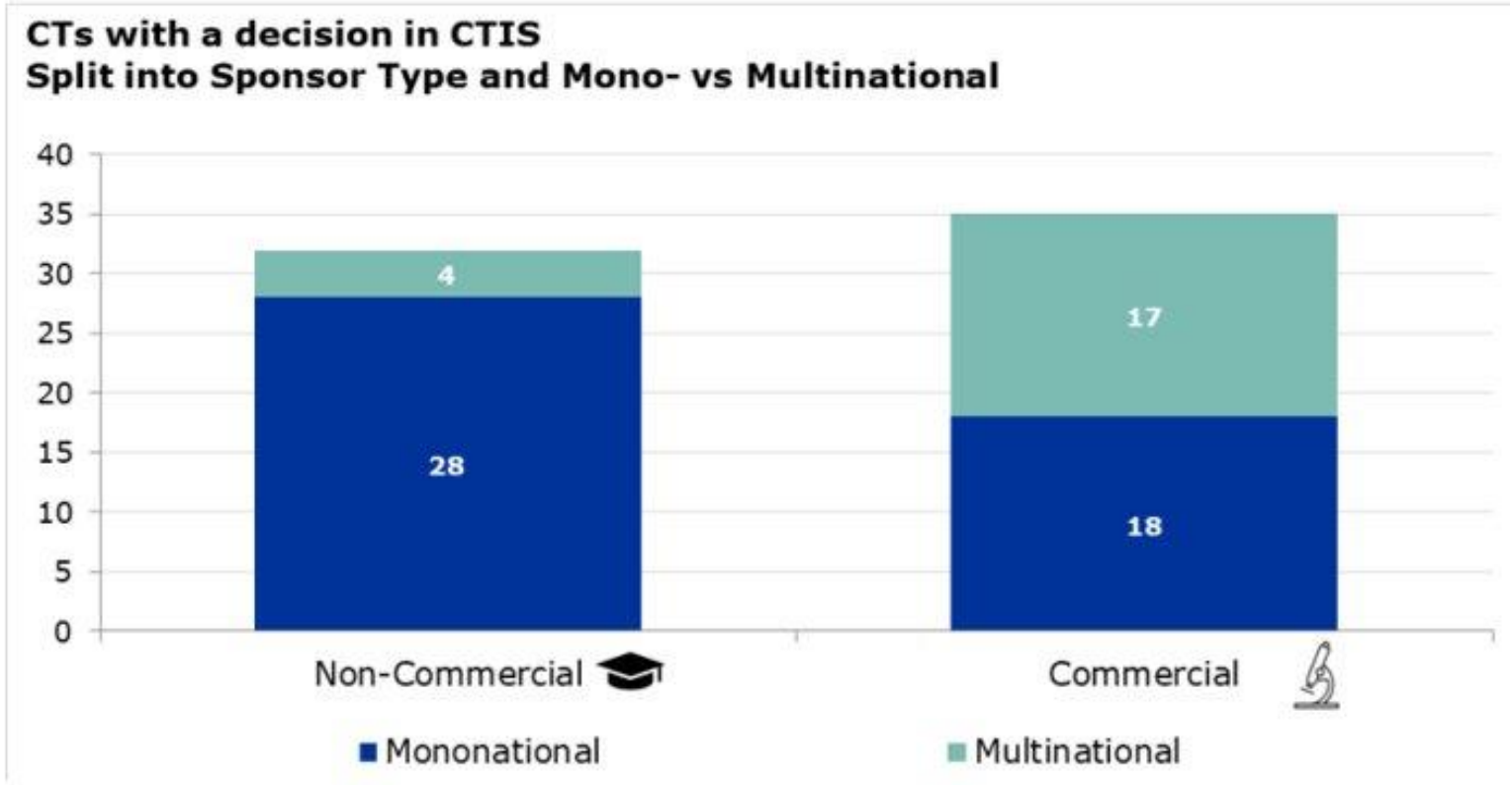


Total CTIS Decisions per month

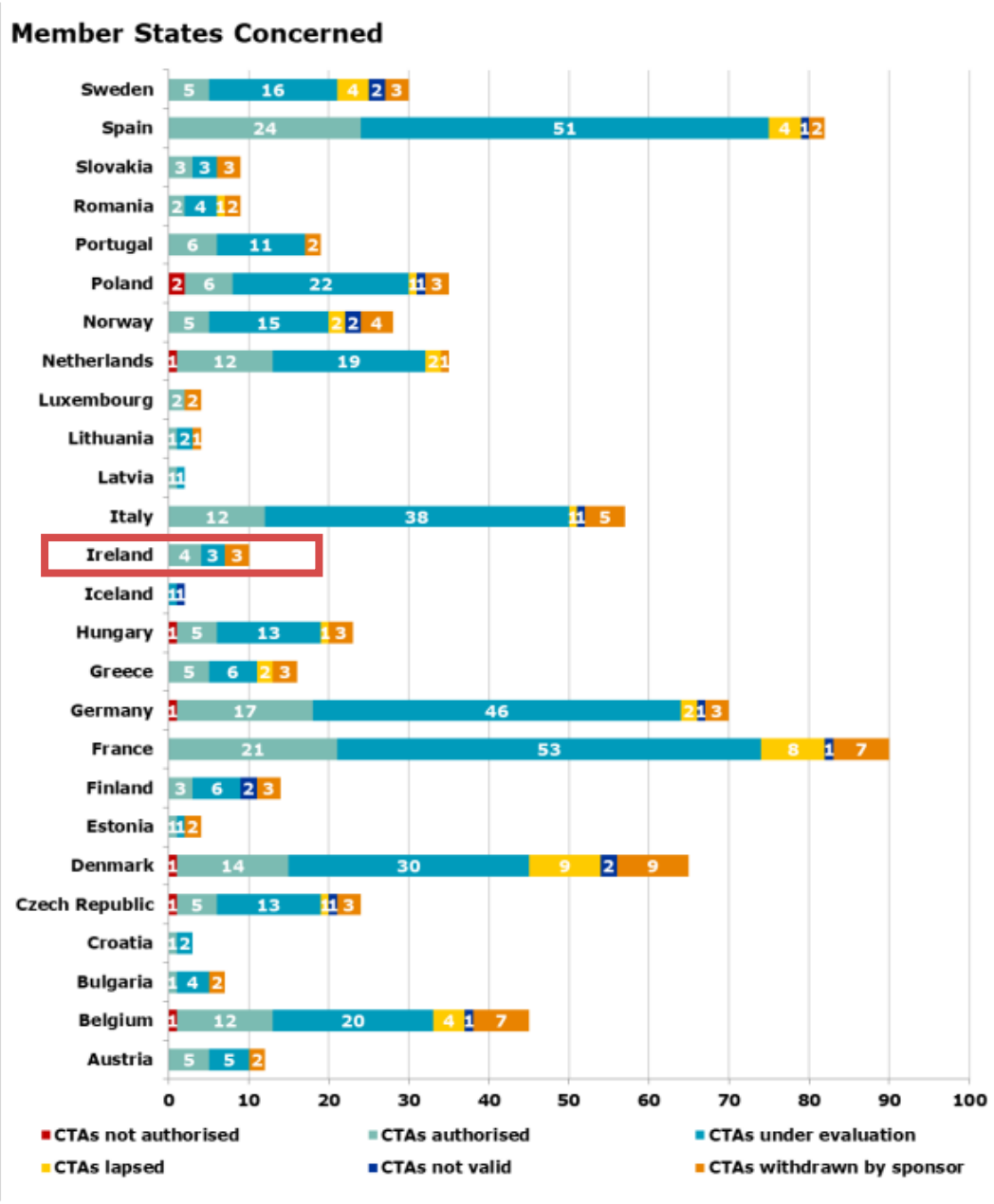


Clinical Trials Regulation: progress on implementation | European Medicines Agency (europa.eu)

CTIS decisions: Commercial versus non-commercial



CTIS Decisions



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National office & NREC experience of CTIS to date

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6 New Applications

- 3 Part I only
- 1 Ireland as RMS
- 3 Part I and Part II

1 Substantial Amendment

- Part I and II

5 Transition trials

National office & NREC experience of CTIS to date

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6 new applications

- COVID-19
- Pandemic response
- Monkeypox
- Epidermolysis bullosa (EB)
- Diffuse cutaneous systemic sclerosis
- IntraCerebral Haemorrhage

CTIS Learnings to date

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Glitches with CTIS system

Straightforward applications dossier

Risk assessment for Part I

EU harmonisation

HPRA meetings and consultations

RMS experience for IE

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NREC-MD

National Research Ethics Committee for Clinical Investigations of Medical Devices and Performance Studies of In Vitro Diagnostic Medical Devices (NREC-MD)

What is a medical device

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Medical devices – key considerations

	Compared to IMPs
Standard clinical development phases	Less standardised Product dependent
Clinical study design	Less standardised
Irreversible effects on study subjects	Common particularly with permanent implants
Types of organisations	Variable, from large to small / start-ups

Drivers of the EU regulatory developments

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- Transparency, harmonisation, coordination
- High-profile failures & recalls (eg Philips Respironics V60 & V60 Plus Ventilators, West Pharmaceutical's fluid transfer systems, Cooks Medical catheters, LeadCare® Blood Lead Test Kits, etc)
- Progress of technology

EU regulatory developments – REC impact

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- Medical Device Regulation (MDR; EU No. 2017/745; SI 260/2021; SI 261/2021), implemented 26 May 2021
- *In Vitro* Diagnostic Medical Device Regulation (IVDR; EU No. 2017/746; SI 256/2022; SI 257/2022), implemented 26 May 2022

Some of the changes:

- Scope and classification of medical devices and in vitro medical devices; EUDAMED; role of economic operators & notified bodies – more details available in HPRA presentations

REC specific changes

- Changes to clinical evaluation processes, including the mandate for national REC review
- Define the remit of the NREC-MD
- Mandate for a single national REC decision
- Review independent from the HPRA review (though we are in regular contact with our colleagues in Medical Devices)

NREC-MD remit

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Defined by the regulations:

- Review of submission of ethics applications relating to clinical investigations (MDR) or performance studies (IVDR)
- Oversight of studies approved under the previous (MDD) and current legislation

Clinical investigations of medical devices (MDR):

- Systematic investigation
- involving one or more human subjects,
- undertaken to assess the safety or performance of a medical device.

Performance studies of in vitro diagnostic medical devices:

- Study
- undertaken to establish or confirm the analytical or clinical performance of an in vitro device;

Types of studies

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Type of study	Examples	MDR	IVDR *
Pre-market	MDR & IVDR • Often undertaken for the purpose of obtaining CE marking IVDR: • Surgically invasive sample-taking • Interventional clinical performance study • Involves additional invasive procedures or other risks • Involves companion diagnostics	A62	A58
Post-market I.	Post market clinical follow-up/ Post market performance follow up • With additional/ burdensome procedures • Outside of the initial CE marking	A74	A70
Post-market II. & other	• Observational studies, eg device registries	A82	A71
Substantial modifications/ amendments	• Change to approved study	A75	

If unsure, please contact us at devices@nrec.ie and the HPRA at devices@hpra.ie

*A57 (left-over samples only) are also subject to REC review

NREC-MD

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	NREC-MD
Remit	Clinical investigations of medical devices (MDR; EU 2017/745) and Performance studies of in vitro diagnostic devices (IVDR; EU 2017/746)
Membership	15 – 28 (quorum of 7), currently 24 members
Meeting frequency	Monthly
Reporting	Minister for Health
Operational support	National Office
Launch	May 2021

Expertise across NREC-MD

- AI, computer science, engineering
- Medicine, nursing, pharmacology, radiology
- Economy
- Ethics, law
- Medical device development & regulatory landscape
- Molecular medicine, genetics
- PPI
- Statistics

https://www.nrecoffice.ie/committees/nrec-md/nrec-md-members/

Volume of applications to date

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Year	New applications		Substantial amendments		Total		Total
	Received & deemed invalid	Reviewed by NREC-MD	Received & deemed invalid	Reviewed by NREC-MD	Received & deemed invalid	Reviewed by NREC-MD	**All**
2021	8	10	2	7	10	17	**27**
2022	24	28	1	13	25	41	**66**
Total	**32**	**38**	**3**	**20**	**35**	**58**	**93**

Volume of applications to date

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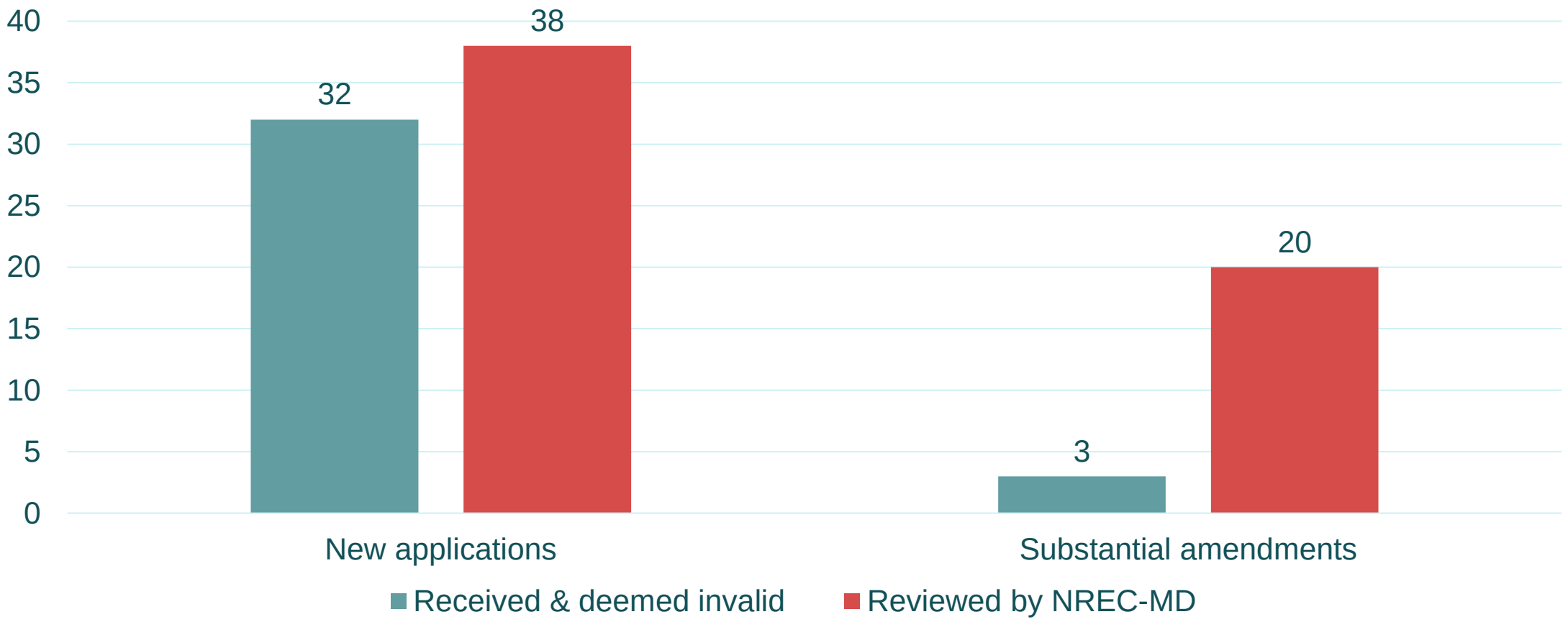

*To date, the National Office has received one IVDR application deemed invalid, we anticipate their resubmission before the end of 2022

Number of final decisions following first NREC review vs RFFIs

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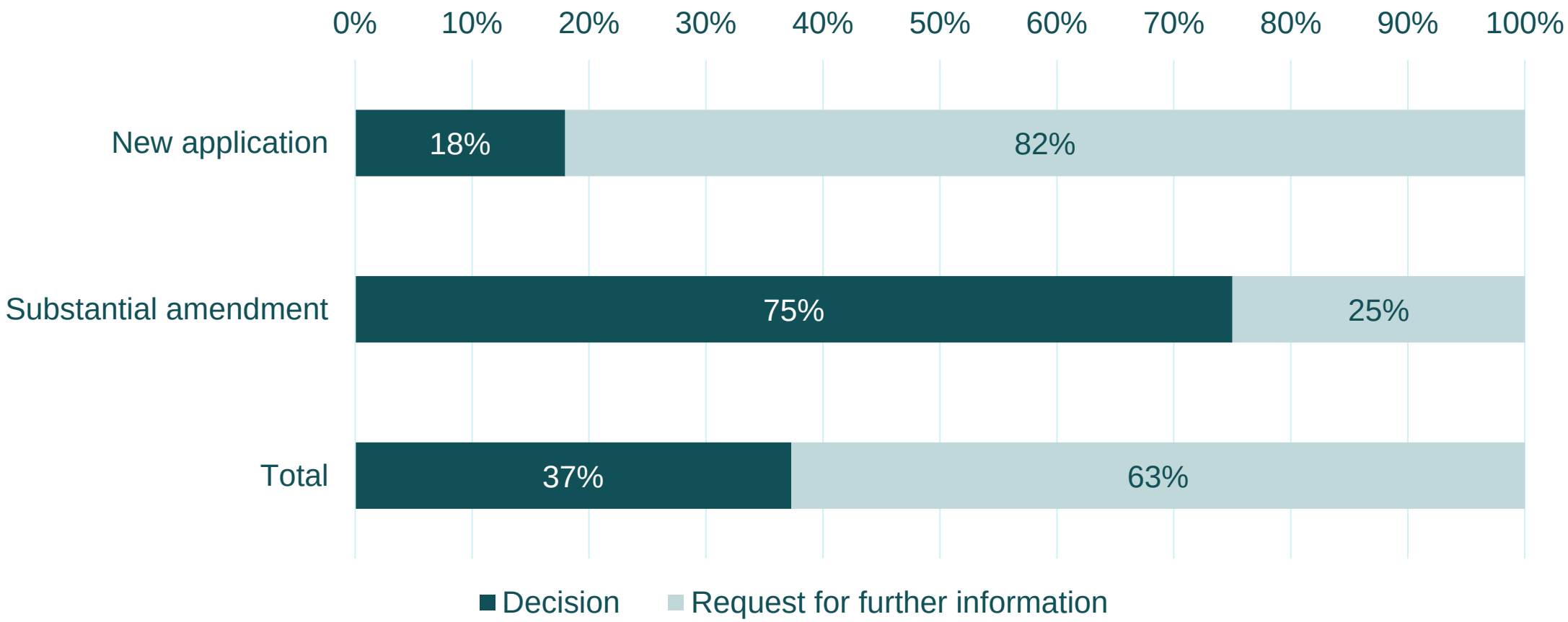

Overview of decisions

Average time from submission to decision: 33 days

Spotlight on key areas

- Based on questions submitted by participants
- Snapshot
- NO observations

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How does the NREC review process work?

NREC review process

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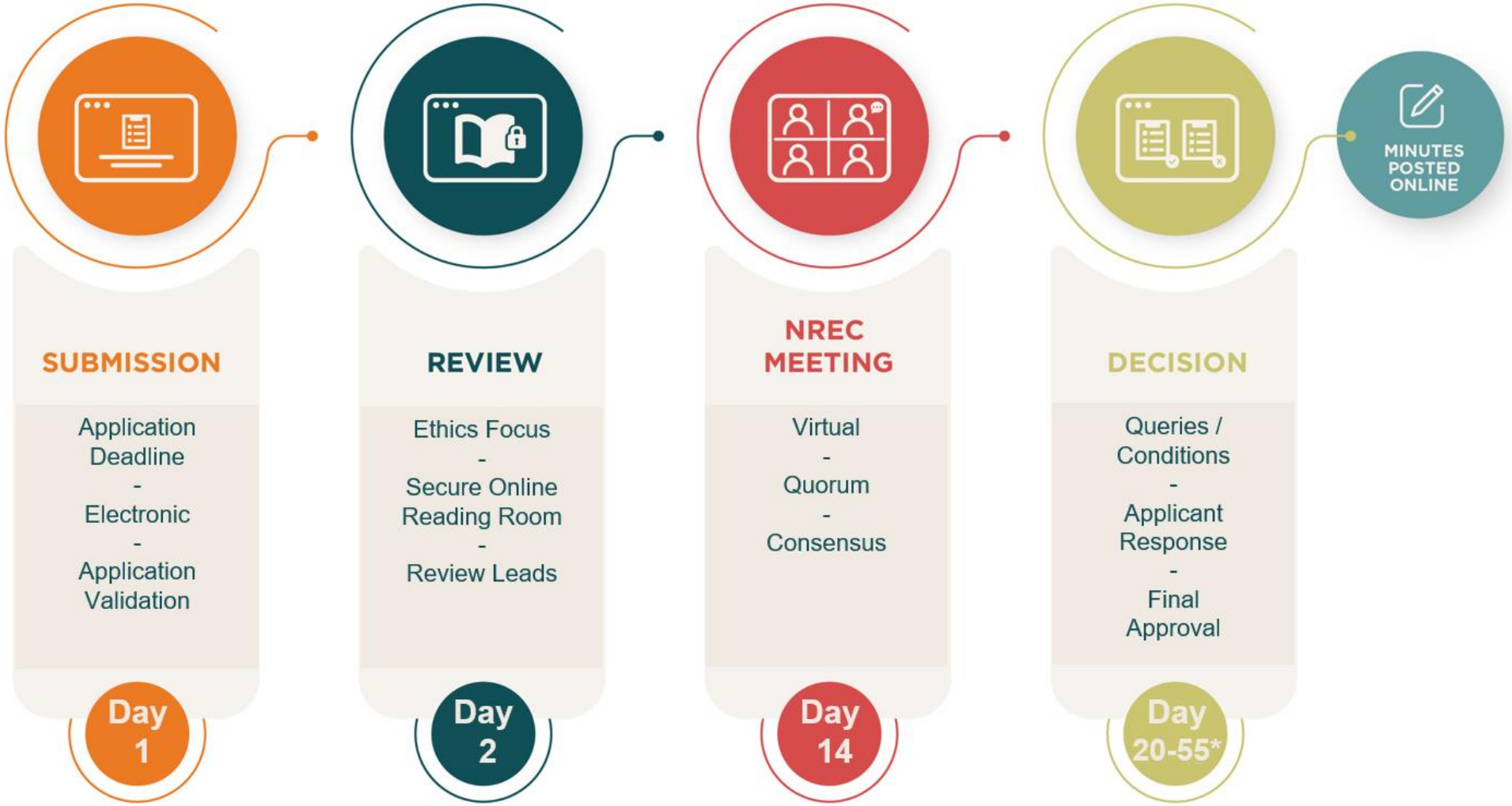


Indicative timing by way of example, stipulated by the EU regulations: 20-55/60 days

NREC review process

- National Office team responds to any queries prior to submission
- Application deadline set approximately 2 weeks before the next Committee meeting
- National Office team reviews the submitted applications to ensure that only valid applications are put forward for NREC review (~850 applications since May 2021)

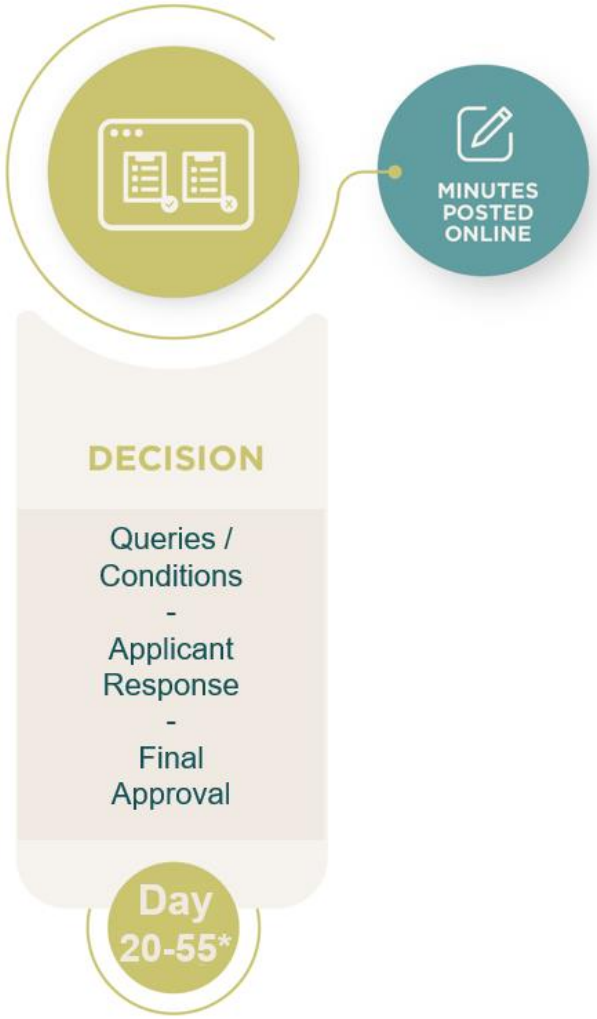
NREC review process

- NRECs receive an agenda and documentation via secure reading room approximately 10 days before the meeting
- Each application is assigned reviewers
- All members have awareness of all applications

NREC review process

- Virtual meetings
- Quorate meetings (minimum seven members, including a Chairperson/ Deputy Chairperson)
- The Committee as a whole arrives at an NREC decision:
  - Favourable opinion
  - Favourable opinion with conditions
  - Unfavourable opinion
  - Request for further information (generally 14 days to respond in order to bring the response to the next meeting & meet timelines outlined in the Regulations)

NREC review process



- National Office drafts letters, once approved, these are sent to applicants
- Applicants have 10 days to accept the decision/ conditions or indicate if they intend to appeal the decision (MDR)
- Responses to request for further information are reviewed at the next meeting (NREC-MD) or offline/ at subgroup meeting (NREC-CT)
- Meeting minutes are published on the website once approved at the subsequent meeting
- Decisions on applications are posted on our website

Combination studies

Combination studies

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- Medicinal products used in combination with a medical device
- Usually the device is used to enable the delivery of the medicine
- Certain types of combination studies are subject to authorisation by both CT and MD team of the HPRA, and are subject to review by both NREC-CT and NREC-MD
- Currently, this review is carried out separately by the two Committees

- Experience to date: *CONNected Electronic Inhalers Asthma Control Trial 3 ("CONNECT 3"), a 24-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison Study of Standard of Care Treatment Versus the Budesonide/Formoterol Digihaler Digital System, to Optimize Outcomes in Adult Patients with Asthma* led by Prof Costello (Beaumont Hospital) & sponsored by Teva Branded Pharmaceutical Products R&D, Inc.

https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices#medicinal-products-used-in-combination-with-a-medical-device-section

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Data protection

Data protection for studies reviewed by NRECs

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- All research that involves the processing of any personal data must be able to demonstrate compliance with both legal requirements and ethical principles, eg EU General Data Protection Regulation (GDPR) the Data Protection Act 2018 (Section 36(2)) (Health Research) Regulations 2018
- The NRECs need to be assured that the legally compliant data protection measures are in place for a each study to safeguard the interests of participants

Data Protection Impact Assessment (DPIA)

- Used to identify and mitigate against data protection-related risks arising from the conduct of a proposed research study
- Mandatory requirement under GDPR and the Data Protection Act 2018 (Section 36(2)) (Health Research) Regulations 2018 for studies that are deemed ‘high risk’ for the processing of personal data - almost all studies falling under the NREC remit
- Completed by the Data Controller of the study and reviewed by relevant Data Protection Officer (DPO). The advice of the DPO must be documented as part of the DPIA process

NREC guidance on data protection for research purposes for applicants
HSE Research and Development Events (08/06/2022 & 14/06/2022)

Consent & capacity

Aspects of consent in health research

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Consent to participate

- Consent can only ever be valid where it is informed, freely given and the person giving it has the capacity to consent.
- Participant encouraged to choose and involve someone with whom they have an on-going close relationship and who is familiar with their will and preferences, beliefs, and values: not a form of legal consent
- Enrolment of prospective participants who lack the capacity to consent on a Clinical Trial of Investigational Medicinal Products (CTIMPs): A 'legally designated representative' (as defined under S.I. 99/2022) may provide consent on behalf of that individual to participate in the CTIMP
- 'Impartial witness' cannot consent on behalf of a participant under Irish law.

Consent for data processing

- Only the person themselves can provide consent for the processing of their personal data.

- If explicit consent is not or cannot be obtained:

1. anonymised data may be processed only, or
2. the researcher must seek a consent declaration from the Health Research Consent Declaration Committee, who must be satisfied that the public's interests in carrying out the research significantly outweighs the requirement for explicit consent of the individuals

Valid consent & consent for future use

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Aspects of valid consent

- Informed
- Specific: named, unambiguous & granular
- Unbundled
- Freely given
- Easy to withdraw
- Recorded

Facilitated through participant facing documentation, eg Participant Information Leaflet

What about future use of data & samples?

- *"I give my permission for data to be stored and for possible future research unrelated to the study without further consent"*
- Blanket consent is not valid
- Consent must continue to be as specific, explicit, and informed as possible, insofar as this is foreseeable
- Recommend to seek consent in a tiered format to give the participant as much choice as possible

Specific considerations

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- Capacity to consent in adults, emergency situations, children
- In such applications, the documentation should clearly outline:
  - Approach to capacity
  - The process of determining capacity
  - Include all relevant consent/ assent forms
  - Any safeguards in place
  - How will compliance with the relevant EU and national regulations as well as policies, eg the HSE National Consent Policy be achieved

Common clarifications required by the NRECs

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- Transparency around transfer of personal data to third countries or other organisations
- Point in the study where personal data is coded or anonymised
- Reference to the Data Protection Act 2018 Health Research Regulations in participant materials
- Reference to rules and regulations from other jurisdictions (mainly UK)
- Separation of consent for study participation and data processing
- Consistency around data retention periods
- Consent vs assent for 16-18 year olds

Role of gatekeeper

Role of gatekeeper

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Safeguard to minimise any perception of coercion and to further facilitate informed consent

Prospective participants initially approached about participation in the study by personnel not directly involved in the direct provision of their health care (eg research nurse) & receive a copy of the participant information leaflet

Information supplied to prospective participants must be understandable and comprehensible to allow them to independently understand and consider the study

Offered an opportunity to discuss any queries on the study with the site PI

Prospective participants revert to the independent research assistant for the consenting process. Site PI should not be involved in the consent aspect of the study.

“Vulnerable” participants

Eg: participants in emergency situations, with diminished capacity, minors, pregnant/ breastfeeding

“Vulnerable” participants

- NRECs value and encourage inclusion in the conduct of studies

For consideration:

- Justification of inclusion/ exclusion
- Compliance with relevant regulations
- Safeguards
- Implications on consent and data processing
- Any additional documentation (assent forms)

Reporting requirements

Safety notifications and corrective measures

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Clinical Trials Directive/ SI190 (Transition period)

- Notify NREC-CT of SUSARS and DSURs
- Annual progress & safety reports submitted on NREC Templates
- Notify recognised RECs of SUSARs and DSURs where study has not transitioned to NREC system.
- No role in corrective measures.

Clinical Trial Regulation

- HPRA leads on the assessment of safety notifications
- NREC-CT involvement at the request of HPRA
- No notification required outside of CTIS
- NREC-CT to work with HPRA on corrective measures

Medical Devices Regulation

- Annual progress & Annual safety reports submitted on NREC Templates
- SUSARs, DSURs, urgent safety measures, protocol deviations
- End of study notification & report

What are some common reason why applications are deemed invalid?

Application validation

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- All relevant documentation listed in the application checklist is included
- Signatures present
- Documents are accessible
- If a document is not included, justification is provided
- For substantial amendment – justification for the amendment is provided
- Application fee paid

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What are some of the typical NREC considerations?

Typical NREC considerations

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- **Application documentation**

  eg Comprehensively completed in an accessible language

- **Scientific design and conduct of the study**

  eg Appropriateness of the study design in relation to study objectives
  Criteria for suspending or terminating research
  Adequacy of the PI and site including support staff, facilities and emergency procedures evidence of relevant experience & training (eg GCP)
  Justification of predictable risks & inconveniences vs anticipated benefits
  Duplicity of / misinformed research effort

- **Recruitment of participants**

  eg Initial contact and recruitment
  Inclusion and exclusion criteria (Unjustified exclusion of vulnerable groups?)

- **Care and protection of participants/**

  eg Insurance & indemnity agreements
  Financial arrangements, participant compensation

Typical NREC considerations

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- **Protection of confidentiality of participants/volunteers**

  eg Extent to which the information will be anonymised

  How long samples/data will be kept

  Security of online tools

  DPIA & DPO input

- **Informed consent process**

  eg Comprehensiveness and understandability of written & oral information

  Identification of those responsible for obtaining consent (risk of coercion, power relationships)

  Arrangements for vulnerable participants

  Aligned with Data Protection Act 2018

- **Community considerations**

  eg Impact & relevance on the local community and on the concerned communities from which participants/volunteers are drawn

  Description of the availability and affordability of any successful study product to the concerned communities following the research

  Plans to disseminate outcomes

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Questions

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Enabling a trusted national ethics opinion