Decentralised elements in Clinical Trials

3rd National Meeting on Clinical Research & Biomedical Innovation (ENICIB)

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The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking (H2020-JTI-IMI2) Trials@Home grant n° 831458.

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The research leading to these results was conducted as part of the Trials@Home consortium. This presentation only reflects the personal view of the stated authors and neither IMI nor the European Union, EFPIA, or any Associated Partners are responsible for any use that may be made of the information contained herein.

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Trials@Home project

The aim

Provide recommendations on Decentralised Clinical Trials (DCT) approaches in Europe

Project start September 1, 2019, due to end November 30, 2025

The consortium

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What are Decentralised Clinical Trial (DCT) approaches?

"operational model in which trial activities are designed to take place at or in the vicinity of the participant's home"

"rather than at a traditional clinical site"

"This approach may make use of technologies and other innovative operational approaches to facilitate data collection"

Santa-Ana-Tellez et al. Decentralised, patient-centric, site-less, virtual, and digital clinical trials? From confusion to consensus. https://doi.org/10.1016/j.drudis.2023.103520

- Not a methodology
- Can be fully decentralised or hybrid
- Can be steered towards pragmatic or towards explanatory methodology

- Better recruitment and retention?
- Lower participant and site burden?
- Lower costs?
- RWE opportunities:
  - More representative study population?
  - Less interference with routine clinical practice?

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Recommendations on decentralised elements in CTs

From European Medicines Regulatory Network, Published Dec 14, 2022 on Eudralex Vol. 10

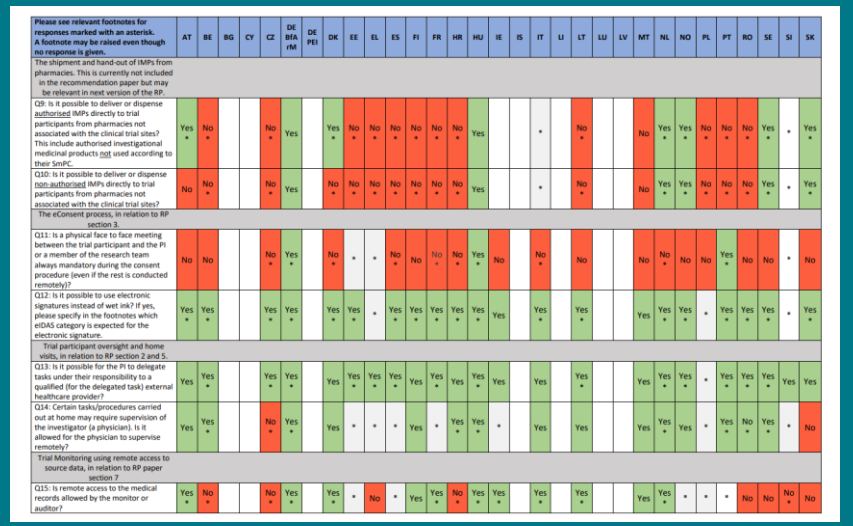
DCT Recommendation paper

Direction of EMRN harmonisation

1. Introduction, scope, general considerations
2. Clinical trial oversight: roles & responsibilities
3. Informed consent process
4. Delivery of medicinal products & administration at home
5. Trial related procedures at home
6. Data collection and management incl. defining & handling source data
7. Trial monitoring

National provisions overview

Member state specific provisions, where national legislation does not currently allow for alignment



Please see relevant footnotes for responses marked with an asterisk. A footnote may be raised even though no response is given.	AT	BE	BG	CY	CZ	DE BfArM	DE PEI	DK	EE	EL	ES	FI	FR	HR	HU	IE	IS	IT	LI	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK
The shipment and hand-out of IMPs from pharmacies. This is currently not included in the recommendation paper but may be relevant in next version of the RP.																															
Q9: Is it possible to deliver or dispense authorised IMPs directly to trial participants from pharmacies not associated with the clinical trial sites? This include authorised investigational medicinal products not used according to their SmPC.	Yes *	No *			No *	Yes		Yes *	No *	No *	No *	No *	No *	No *	Yes			*		No *			No	Yes *	Yes *	No *	No *	No *	No *	Yes *	*	Yes *
Q10: Is it possible to deliver or dispense non-authorised IMPs directly to trial participants from pharmacies not associated with the clinical trial sites?	No	No *			No *	Yes		No *	No *	No *	No *	No *	No *	No *	Yes			*		No *			No	Yes *	Yes *	No *	No *	No *	No *	Yes *	*	Yes *
The eConsent process, in relation to RP section 3.																															
Q11: Is a physical face to face meeting between the trial participant and the PI or a member of the research team always mandatory during the consent procedure (even if the rest is conducted remotely)?	No	No			No *	Yes *		No *	*	*	No *	No	No	No *	Yes *	No		No *		No			No	No *	No	No	Yes *	No	No	*	No
Q12: Is it possible to use electronic signatures instead of wet ink? If yes, please specify in the footnotes which eIDAS category is expected for the electronic signature.	Yes *	Yes *			Yes *	Yes *		Yes *	Yes *	*	Yes *	Yes *	Yes *	Yes *	Yes *	Yes		Yes *		Yes *			Yes	Yes *	Yes *	*	Yes *	Yes *	Yes *	*	Yes *
Trial participant oversight and home visits, in relation to RP section 2 and 5.																															
Q13: Is it possible for the PI to delegate tasks under their responsibility to a qualified (for the delegated task) external healthcare provider?	Yes	Yes *			Yes *	Yes *		Yes	Yes *	Yes *	Yes *	Yes	Yes *	Yes	Yes *	Yes		Yes		Yes *			Yes	Yes *	Yes *	*	Yes *	Yes *	Yes *	Yes	Yes
Q14: Certain tasks/procedures carried out at home may require supervision of the investigator (a physician). Is it allowed for the physician to supervise remotely?	Yes	Yes *			No *	Yes *		Yes	*	*	*	Yes	*	Yes *	Yes *	*		Yes		Yes			Yes	Yes *	Yes	*	Yes *	No *	Yes *	*	No
Trial Monitoring using remote access to source data, in relation to RP paper section 7																															
Q15: Is remote access to the medical records allowed by the monitor or auditor?	Yes *	No *			No *	Yes *		Yes *	*	No	*	Yes	Yes *	No *	Yes *	Yes *		Yes *		Yes *			Yes	Yes *	*	*	*	No	No	No *	No

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RADIAL PROOF-OF-CONCEPT STUDY

Aim:
To assess the scientific and operational quality of a fully decentralised and hybrid trial approach compared to a conventional trial approach

Approved proof-of-concept study

Methodological objective: KPIs as main outcomes

Low intervention phase IV trial

Toujeo® used within market authorization label

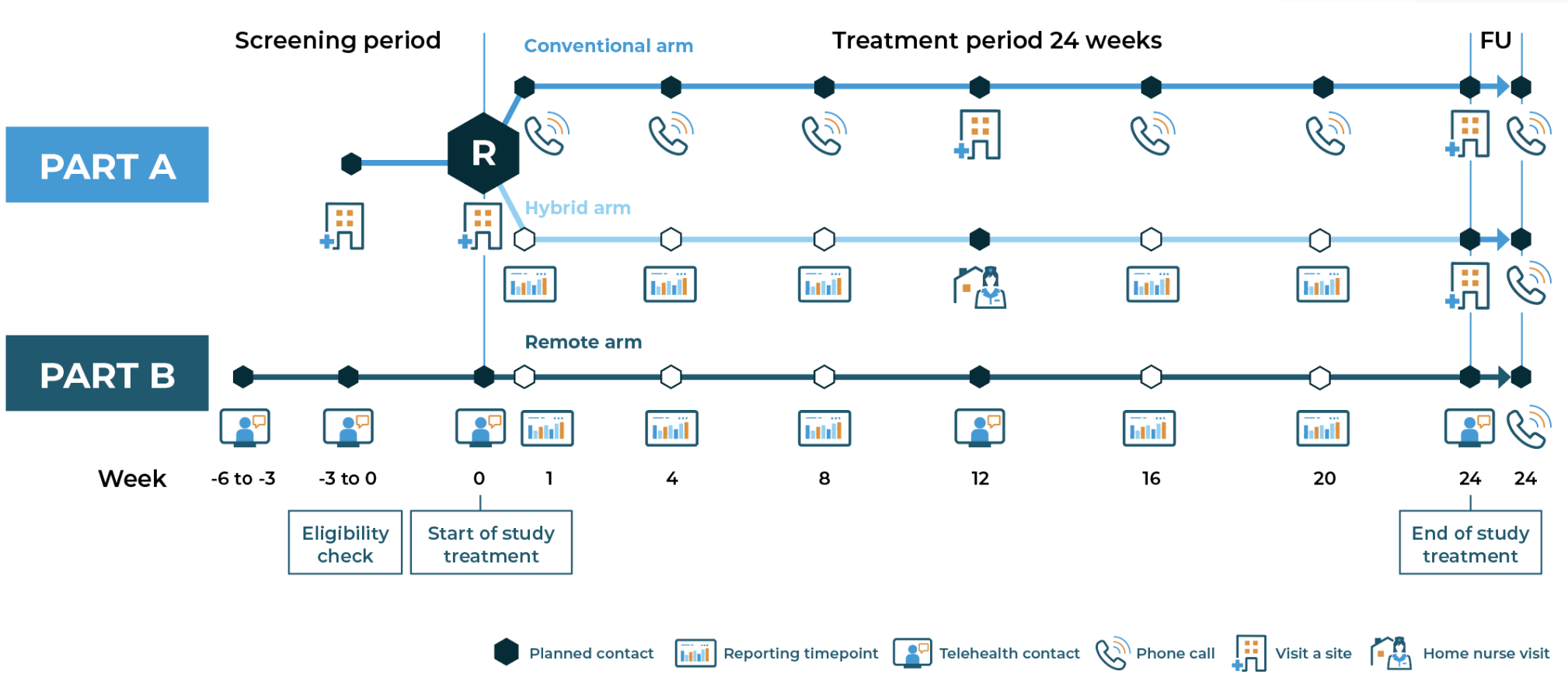
Population familiar with insulin use

People with DM2 treated with basal insulin with HbA1c 7-10%

<u>Acceptability:</u> safety, data quality and medical endpoints
<u>Potential benefits:</u> subject retention, recruitment, diversity, cost, site & patient satisfaction

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking (H2020-JTI-IMI2) Trials@Home grant n° 831458.

Set-up of RADIAL proof-of-concept study



Countries

- Poland
- Germany
- UK
- Denmark
- Spain
- Italy

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Decentralised elements in RADIAL

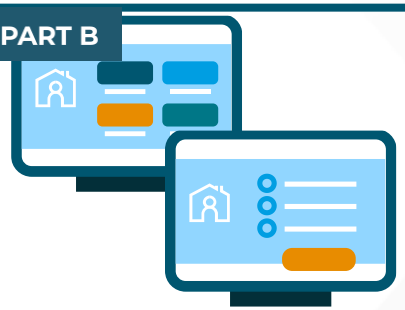
PART B

eConsenting and eSignature

PART B

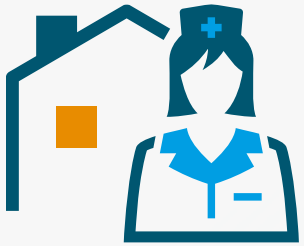
Telemedicine

PART B



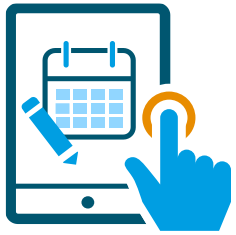
Online recruitment and pre-screening

PART A



Home nurse visits

Remote monitoring IMP adherence



Study app for reporting (S)AEs and ePROs

Direct to patient shipment of IMP

At home sample collection

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking (H2020-JTI-IMI2) Trials@Home grant n° 831458.

Informed Consent

The eConsent process, in relation to RP section 3.																
Q11: Is a physical face to face meeting between the trial participant and the PI or a member of the research team always mandatory during the consent procedure (even if the rest is conducted remotely)?	No	No			No *	Yes *		No *	*	*	No *	No	No *	No *	Yes *
Q12: Is it possible to use electronic signatures instead of wet ink? If yes, please specify in the footnotes which eIDAS category is expected for the electronic signature.	Yes *	Yes *			Yes *	Yes *		Yes *	Yes *	*	Yes *	Yes *	Yes *	Yes *	Yes *

Q11	Dialogue is mandatory
Q12	On a case-by-case basis; wet ink use should also be possible, along with e-signatures; accord eID sample implementation software is described as being implemented in Portugal; please

RECOMMENDATION PAPER ON DECENTRALISED ELEMENTS IN CLINICAL TRIALS: Published Dec 14th 2022 on Eudralex Vol. 10

- ICH E6: trial participants fully informed and able to ask q
- Remote informed consent may be justified, case-by-case intervention, trial complexity etc.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 March 2023
EMA/INS/GCP/112288/2023
Good Clinical Practice Inspectors Working Group (GCP IWG)

Guideline on computerised systems and electronic data in clinical trials

Adopted by GCP IWG for release for consultation	4 March 2021
Start of public consultation	18 June 2021
End of consultation (deadline for comments)	17 December 2021
Final version adopted by the GCP IWG	7 March 2023
Date of coming into effect	6 months after publication

This guideline replaces the 'Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials' (EMA/INS/GCP/454280/2010).

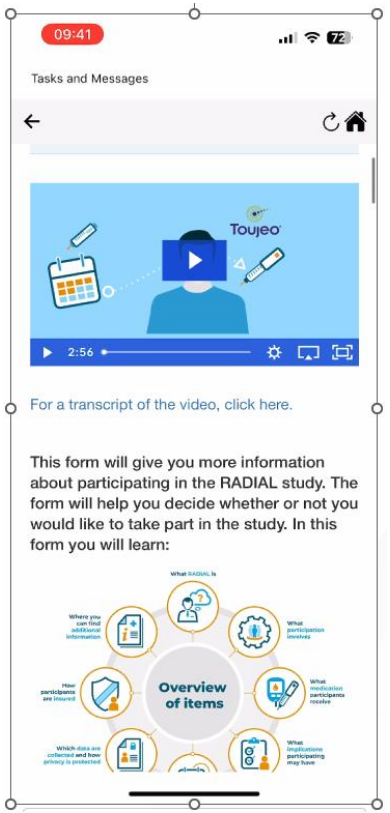
Keywords	***Computerised systems, electronic data, validation, audit trail, user management, security, electronic clinical outcome assessment (eCOA), interactive response technology (IRT), case report form (CRF), electronic signatures, artificial intelligence (AI)***

The research leading to these results has received support from th

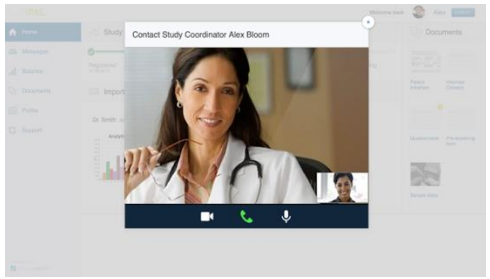
RADIAL part B consent - Participant Experience

Clinpal eConsent solution with Qualified Electronic Signature

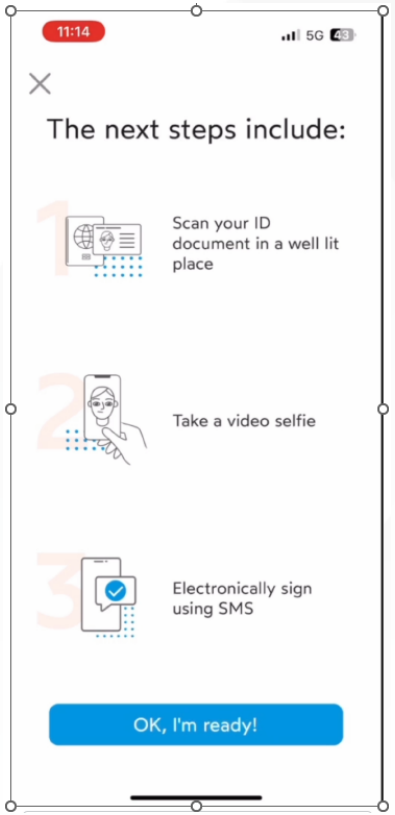
Informing (watch, read, quiz, check willingness to proceed)



Consultation (video call with site)



Signature (opt-ins, identity, signing, download)



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Clinical trial oversight

Trial participant oversight and home visits, in relation to RP section 2 and 5.																																		
																																PT				
Q13: Is it possible for the PI to delegate tasks under their responsibility to a qualified (for the delegated task) external healthcare provider?	Yes	Yes *			Yes *	Yes *		Yes	Yes *	Yes *	Yes *	Yes	Yes *	Yes	Yes *	Yes		Yes		Yes *			Yes	Yes *	Yes *	*	Yes *	Yes *	Yes *	Yes	Yes
Q14: Certain tasks/procedures carried out at home may require supervision of the investigator (a physician). Is it allowed for the physician to supervise remotely?	Yes	Yes *			No *	Yes *		Yes	*	*	*	Yes	*	Yes *	Yes *	*		Yes		Yes			Yes	Yes *	Yes	*	Yes *	No *	Yes *	*	No

Q13	Healthcare provider must be in direct dependency of the IP
Q14	Should be clearly specified in the CT protocol

RECOMMENDATION PAPER ON DECENTRALISED ELEMENTS IN CLINICAL TRIALS: Published Dec 14th 2022 on Eudralex Vol. 10

- ICH E6 responsibilities stay the same
- Ensure that sponsor and investigator are able to keep oversight on trial paticipant safety and well-being

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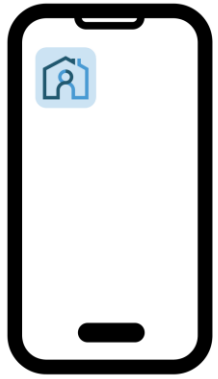
How to maintain oversight when participants are remote?

- In decentralised/hybrid arm, the investigator has access to tools to maintain oversight – even though the participant does not physically visit the site.

Remote

Data collection



Continuous reporting

Remote

monitoring

(Ad hoc)

Telemedicine or phone call

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A remote site, a 24/7 clinical trial site?

- We cannot expect real-time review and follow-up on collected data and reports
- Risk-based approach
- Expectation management (for both site and participant)

Weekly ‘digests’ of dosing data

Automated alerts for possible SAEs

Reporting timepoints

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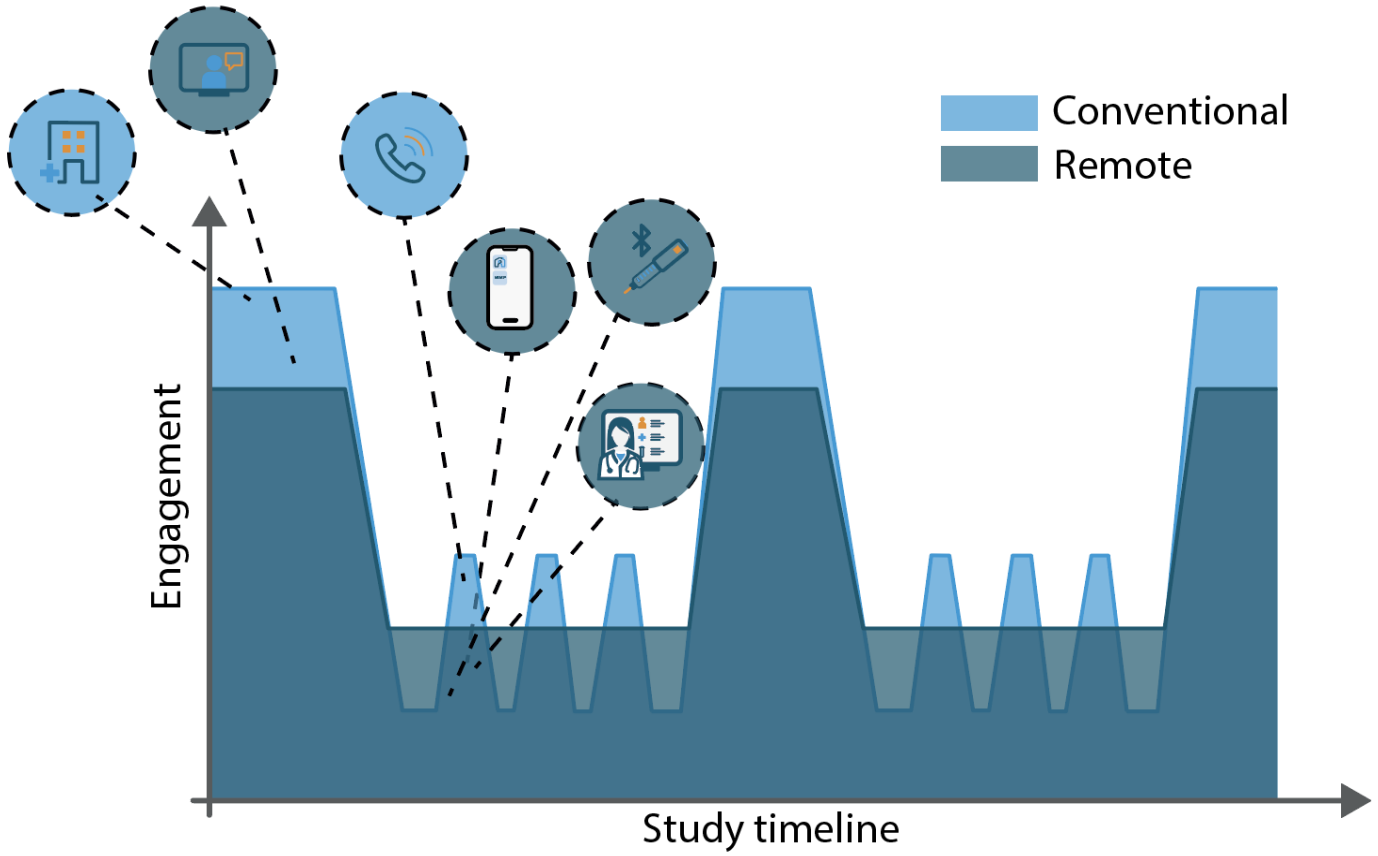
Investigator oversight in a DCT (RADIAL)

- In a conventional trial, the participant is most of the time 'remote' (not at the clinical trial site).
- Using (novel) technology the remote participant can be brought 'closer' to the investigator



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Direct-to-Participant (DtP) shipment of IMP

RECOMMENDATION PAPER ON DECENTRALISED ELEMENTS IN CLINICAL TRIALS

Version 01, 13 December 2022

DELIVERY OF INVESTIGATIONAL MEDICINAL PRODUCTS AND ADMINISTRATION AT HOME

Where it is intended for the IMP4 to be delivered and/or administered at the trial participant's home, a risk assessment should be completed to determine if such an approach is appropriate.

The investigator remains responsible for the decision of treatment which should be documented prior to any delivery of IMP to the trial participant's home

There are several options for delivery of the IMP to the trial participant's home, depending on what is permitted by national requirements. This can include delivery from the pharmacy of the investigator site, from a delegated pharmacy, or from a depot. The sponsor has the overall responsibility for the process and the contracts or agreements, which should reflect the principal investigator's responsibilities pursuant to ICH E6.

The sponsor should ensure that the personal data of the trial participants required for the delivery of the IMP is used in accordance with the GDPR on a need-to-know basis.

https://health.ec.europa.eu/system/files/2023-03/mp_decentralised-elements_clinical-trials_rec_en.pdf

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Direct-to-Participant (DtP) shipment of IMP

Please see relevant footnotes for responses marked with an asterisk. A footnote may be raised even though no response is given.	AT	BE	BG	CY	CZ	DE BfArM	DE PEI	DK	EE	EL	ES	FI	FR	HR	HU	IE	IS	IT	LI	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK
The delivery of IMPs from sponsor/site, in relation to RP section 4.																															
Q1: Is it possible to deliver IMPs directly to trial participants from their associated trial site?	No *	No *			Yes *	Yes *		Yes	Yes	*	Yes *	Yes	*	No *	Yes	Yes		Yes		Yes *			Yes *	Yes *	Yes	Yes	Yes *	Yes	Yes *	No *	Yes
Q2: Is it possible to deliver IMPs directly to trial participants from the pharmacy associated with the trial site?	No *	No *			Yes *	Yes *		Yes	No *	*	Yes *	Yes *	*	No *	Yes			Yes		No *			Yes *	Yes *	Yes	Yes	Yes *	No *	Yes *	*	Yes
Q3: Is it possible to deliver IMPs directly to trial participants from any delegated pharmacy?	No *	No *			Yes *	Yes		Yes *	No *	No *	No *	No *	Yes	No *	Yes			*		No *			No	Yes *	Yes	No *	Yes *	No *	Yes *	No *	Yes
Q4: Is it possible to deliver IMPs directly to trial participants from the IMP manufacturer with a MIA license?	No	No *			No *	No		*	No *	No *	No *	No *	No *	No *	Yes	No *		*		No *			No	No	No *	No *	Yes *	No	No	No *	No
Q5: Is it possible to deliver IMPs directly to trial participants from the trial sponsor (sponsors intermediaries/depots)? If yes, footnote states if a licence is required for the depot to carry out this task and how to obtain this licence.	No	No *			No *	No		*	No *	No *	No *	No *	No	No *	No			*		No			No	No	No *	No *	No *	Yes *	No	*	No
The shipment of IMPs from sponsor/site across boarders within the EU, in relation to RP section 4.																															
Q6: Is it possible to deliver IMPs directly to trial participants from e.g. distribution/manufacturing/pharmacy licence holders located in other EU MSs if legally allowed to carry out this task in the country of origin?	No *	No *			No *	No *		Yes	No *	No *	No *	No *	No *	No *	Yes			*		No *			No	No *	No *	No *	No *	Yes	No *	No *	No
Q7: Is it possible to deliver IMPs directly to investigators from e.g. distribution/manufacturing/pharmacy licence holders located in other EU MSs if legally allowed to carry out this task in the country of origin?																															

Delegated pharmacy in country

Directly from sponsor

Central pharmacy abroad

	PT
Q1	as long as shipping conditions are kept under control
Q2	as long as shipping conditions are kept under control
Q3	to be assessed on a case-by-case basis; IMP circuit should be clearly and in detail described in the CT protocol
Q4	to be assessed on a case-by-case basis; IMP circuit should be clearly and in detail described in the CT protocol
Q5	Article 32nd, Law 21/2014, from the 16th of April, current version
Q6	Article 32nd, Law 21/2014, from the 16th of April, current version
Q7	to be assessed on a case-by-case basis; IMP circuit should be clearly and in detail described in the CT protocol

RECC

TRIALS @HOME

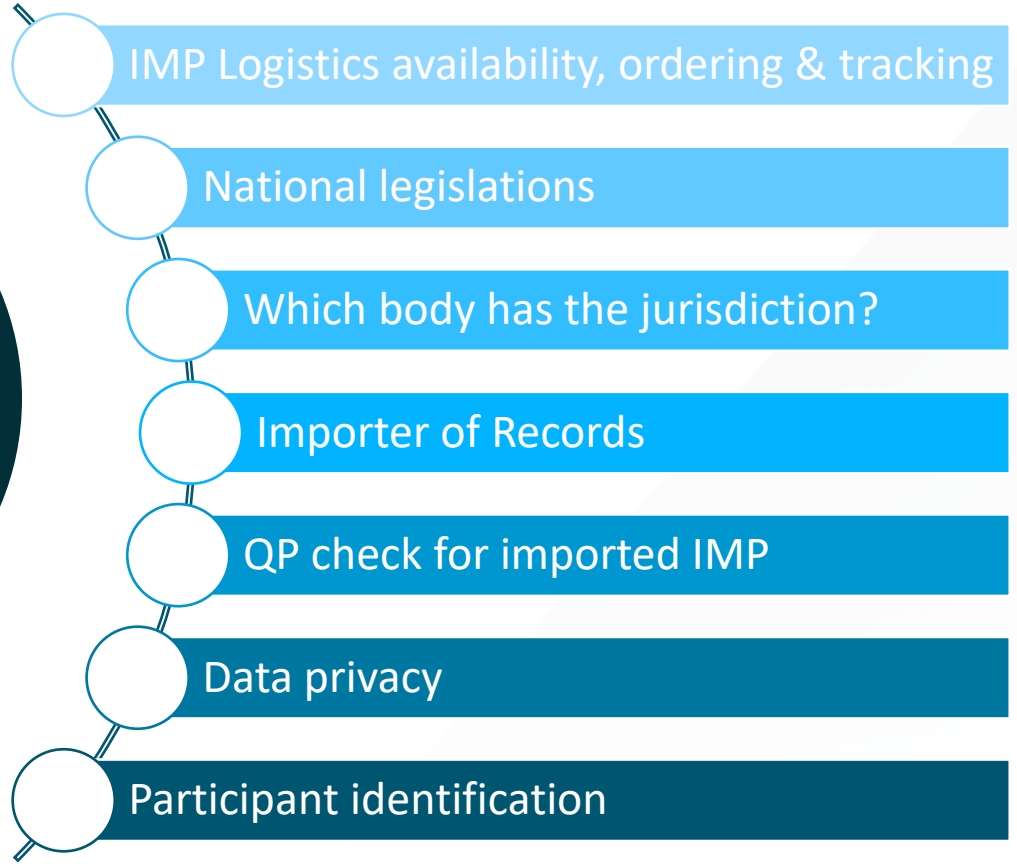
ant n° 831458.

DtP IMP delivery in RADIAL

Protocol approved in CTIS based on one general DtP IMP description

Operationalizing DtP IMP

The devil is in the details



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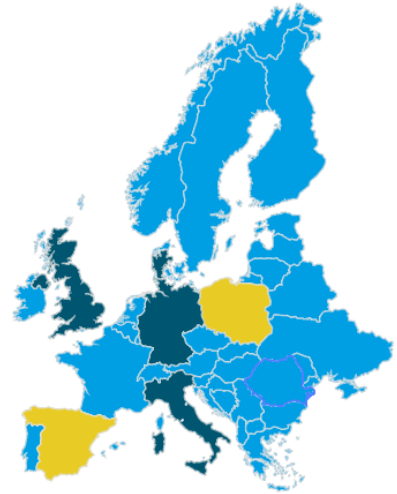
DtP IMP delivery in RADIAL

Tailored approach required



Be clear on what you're talking about → 4 models with difference in acceptance in different countries:

1. Site (pharmacy) – courier – participant
2. Central pharmacy – courier – participant
3. Sponsor – courier – participant → not in RADIAL
4. Local pharmacy – courier – participant → not in RADIAL

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How to move forward?

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Moving from the theoretical to the practical: Many learnings and change accomplished through RADIAL proof-of-concept study

Decentralized Trial Approaches: How Do They Match Up To Conventional Studies?

11 Nov 2022 | INTERVIEWS

by Vibha Sharma

@ScripRegVibha | vibha.sharma@citeline.cc

Executive Summary

Mira Zuidgeest is the principal investigator of a key remote, hybrid and conventional clinical trial appr the study might help understand "where we're hea

European Commission

EMA EUROPEAN MEDICINES AGENCY

HMA Heads of Medicines Agencies

29 September 2022
EMA/789028/2022

ACT EU Multi-stakeholder Meeting on Decentralised Clinical Trials

4 October 2022, 09:30-17:00 CET

EU Regulators Told To 'Normalize' Decentralized Clinical Trials

15 Jan 2024 | NEWS

by Vibha Sharma

@ScripRegVibha | vibha.sharma@citeline.com

Executive Summary

EU drug regulators have received some candid responses from trial sponsors and other stakeholders on the aspects that should be urgently addressed in the next iteration of their guidance on decentralized clinical trials.

Scientists around the world speak to the importance of conducting representative research and show how when people can't make it to a study, the study needs to come to them. With new technologies and novel approaches, it is becoming increasingly evident that the way we conduct research can matter as much as the research itself.

Thank you!

Further information on T@H and RADIAL:

Project website www.trialsathome.com
Contact us at trialsathome@umcutrecht.nl
Mira Zuidgeest m.g.p.zuidgeest@umcutrecht.nl

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