Clinical trial roadmap

For participating centers of an Investigator Initiated Study (IIS)

Opgesteld door: Wendy Dontje, DORP

De volgende partijen hebben bijgedragen aan dit document:
Erasmus MC, IKNL, LUMC, NKI-AvL, RadboudUMC, MUMC

Proclaimer

De informatie in dit document is met de grootst mogelijke zorg en aandacht samengesteld door experts uit verschillende disciplines en samengebracht en ter beschikking gesteld vanuit DORP. Bij het samenstellen van de informatie is gebruik gemaakt van verschillende bronnen. Er is rekening gehouden met de op het moment van plaatsen geldende wet- en regelgeving en ethische kaders, en de interpretatie daarvan door de personen en/of organisaties die bijdragen aan DORP. We doen ons uiterste best om alle informatie juist en volledig weer te geven. Komt u desondanks toch iets tegen dat niet correct is of verouderd, dan stellen wij uw reactie bijzonder op prijs.

Inhoud

Introduction 3
Before you start 3
1 Phase 1: Preparation 4
1.1 Feasibility 4
1.2 Budget 4
2 Phase 2: Start up and initiation 5
2.1 Contracts 6
2.2 Site suitability: VGO 6
2.3 Approval 7
2.4 Initiation 7
3 Phase 3: Conduct 9
3.1 Patient inclusion 9
3.2 Study treatment 10
3.3 Data collection 11
3.4 Safety reports: AEs, SAEs, SUSARs, SADEs 11
3.5 Monitoring 12
3.6 Trial closure 12
4 Phase 4: Analysis & publication 13
4.1 Manuscript preparation & publication 13
5 Phase 5: Wrap up 14
5.1 Archiving 14
6 Phase 6: Implementation or follow up research 15
6.1 Implementation 15
6.2 Follow up research 15
7 List of abbreviations 16

Introduction

The Clinical trial roadmap is developed by DORP to optimally support investigator initiated clinical oncological research. It is not unique as most trial and science offices have their own guidelines. This roadmap is however the result of exchanging and combining experience and knowledge of experts from Erasmus MC, IKNL, LUMC, NKI-AvL, RadboudUMC, MUMC. It brings together useful tips, references and links to templates.

The roadmap guides investigators through 6 phases of a clinical trial. It gives an overview of responsibilities and on what needs to be organized. Importantly, at all times it should be used in conjunction with the investigator's local trial/science office.

The to do's differ for the initiating investigator (sponsor) and for participating local investigators. Therefore 2 versions of the roadmap are developed: one with to do's for the sponsor and one with to do's for participating centers. Every clinical trial phase is summarized by an infographic to illustrate the most important actions.

Before you start

This Roadmap is intended as a tool for local investigators of centers participating in a multicenter trial. It is of great importance for a local Principal Investigator (PI) to have a valid BROK or GCP certificate.

Contact the local trial/science office for information about local practice and available services within your institute.

1 Phase 1: Preparation

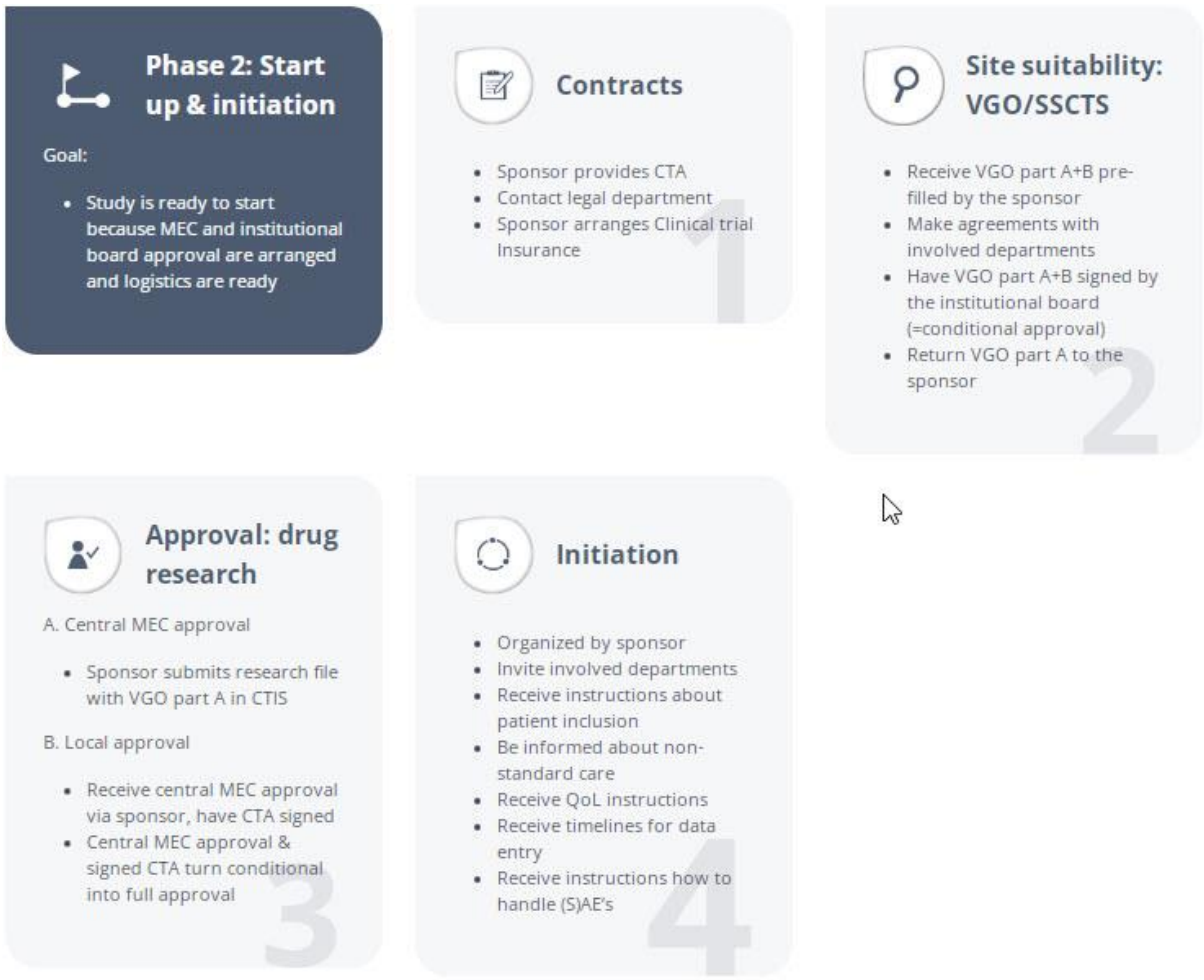
1.1 Feasibility

- The local PI has a valid BROK or GCP certificate or has registered for a BROK or GCP training. Re-register if necessary.
- Determine if the study proposal meets the research focus of your department and if your department supports the study
- Contact the local science office and inquire about the local "research code":
    - The level of support provided by the local science office.
    - Make arrangements about internal logistics (who signs contracts, who sends required documents to the sponsor, who submits the research file to the local registration system and to the institutional board, etc.)
- Prepare a draft budget in consultation with the local science office. In addition to (extra) clinical procedures, also take into account local trial coordination and datamanagement if not arranged centrally.
- Discuss if there is enough capacity to perform the study (do colleagues have time and knowledge to inform and include patients, do other departments such as lab, pathology have enough capacity).
- Determine if the number of required patients is available. In general, divide the number of available patients by half to get a good estimate of the number of participants.

1.2 Budget

- Identify the (extra) costs that will be made in the context of the study, based on the assessment schedule in the protocol and/or the table with (extra) clinical procedures in the VGO provided by the sponsor .
- Make an inventory if there will be costs for local trial coordination, LDM, institutional board approval, local science office.
- Request quotes for the required services (locally at the institute or at a service provider/ trial office).
- **Based on feasibility and budget, decide whether there is a “go or no-go”.**

2 Phase 2: Start up and initiation



From February 2022 onwards, the procedures for local and central approval of *drug research* will change and differ from the procedures for *other research subject to WMO* (overig WMO-plichtig onderzoek):

	Drug research	**Other research subject to WMO**
VGO	Mandatory from November 2021	Recommended from November 2021
OV	Not applicable from November 2021	Still accepted from November 2021
Registration	CTIS (Clinical Trial Information System)	Toetsingonline
Approval	Local (conditional!) followed by central MEC; central MEC approval & signed CTA turn conditional into full approval	OV: Central MEC followed by local VGO: Local (conditional!) followed by central MEC; central MEC approval & signed CTA turn conditional into full approval

The VGO (Verklaring Geschiktheid Onderzoeksinstelling) replaces the Research declaration (OV, Onderzoeksverklaring) and is used to record the outcome of the local feasibility meeting with involved departments about budget, logistics, etc., based on the overview of (extra) procedures provided by the sponsor. For details

see the Local Feasibility procedure of the DCRF. For other research subject to WMO it is recommended to implement the VGO as soon as possible.

2.1 Contracts

- The CTA is an agreement between the sponsor and participating sites and should be provided by the sponsor. The template can be found on the CCMO website. For drug research you will receive:
  - Model research contract for use with VGO
- Use of this template is generally accepted and prevents delays. The local science office can refer to the legal department to check the contract and negotiate if necessary. Leave this to the legal department.
- In case it is expected that patients will be referred to another institute for (part of) the treatment, for example for radiotherapy, the sponsor has to be informed, give permission and needs to make arrangements with that institute.
- In case of referring a patient to a non-participating center (for example for radiotherapy) the board of that institute needs to be informed that study patients are treated in their institute. Check with the sponsor to make the necessary arrangements. The referring local PI is responsible that study procedures and data are recorded in the EPF of that institute and transferred to the local EPF.
- Contracts with other parties (pharmaceutical) should go through the legal department.
- Contracts with internal/external service providers (datamanagement) should go through te legal department.
- Check with the local science office if processor agreements (verwerkersovereenkomsten) with parties that process data are signed. This only applies to external parties that process data and that are not covered by the standard CTA.
- In any case a service is outsourced to subcontractors, the sponsor has to be informed and give permission.
- Start on time with the contracts.
- Clinical trial Insurance: the sponsor is responsible for the Clinical trial Insurance.

2.2 Site suitability: VGO

- Receive a VGO pre-filled by the sponsor.
- In collaboration with the local science office, organize a local feasibility meeting to discuss the trial with involved departments in your institute. Provide sufficient detailed information. Think of the final protocol, list of (extra) procedures, global budget, concept manuals.
- Make agreements with involved departments, document suitability of the institute in VGO appendix and have it signed by involved departments.
- Have the VGO signed by the Institutional Board, thereby declaring the institutes' suitability based on the VGO appendix.

- Return the signed VGO to the sponsor.
- Attention: a signed VGO means conditional Institutional Board approval!

- In general the sponsor appoints an independent physician who can be contacted by patients with questions about the study. Your institute can oblige to appoint a local independent physician. In that case ask for a CV (necessary for MEC) and send it to the sponsor.

2.3 Approval

- The sponsor is responsible for submitting the research file of the study to CTIS for central MEC review and approval.

A. Central MEC approval
- The sponsor submits the research file including VGO (from sponsor and participating centers) and template CTA in the CTIS-portal.

B. Local approval
- The Institutional Board has already given conditional approval by signing the VGO. This is converted into full approval once the MEC has approved the study and when the CTA is signed.

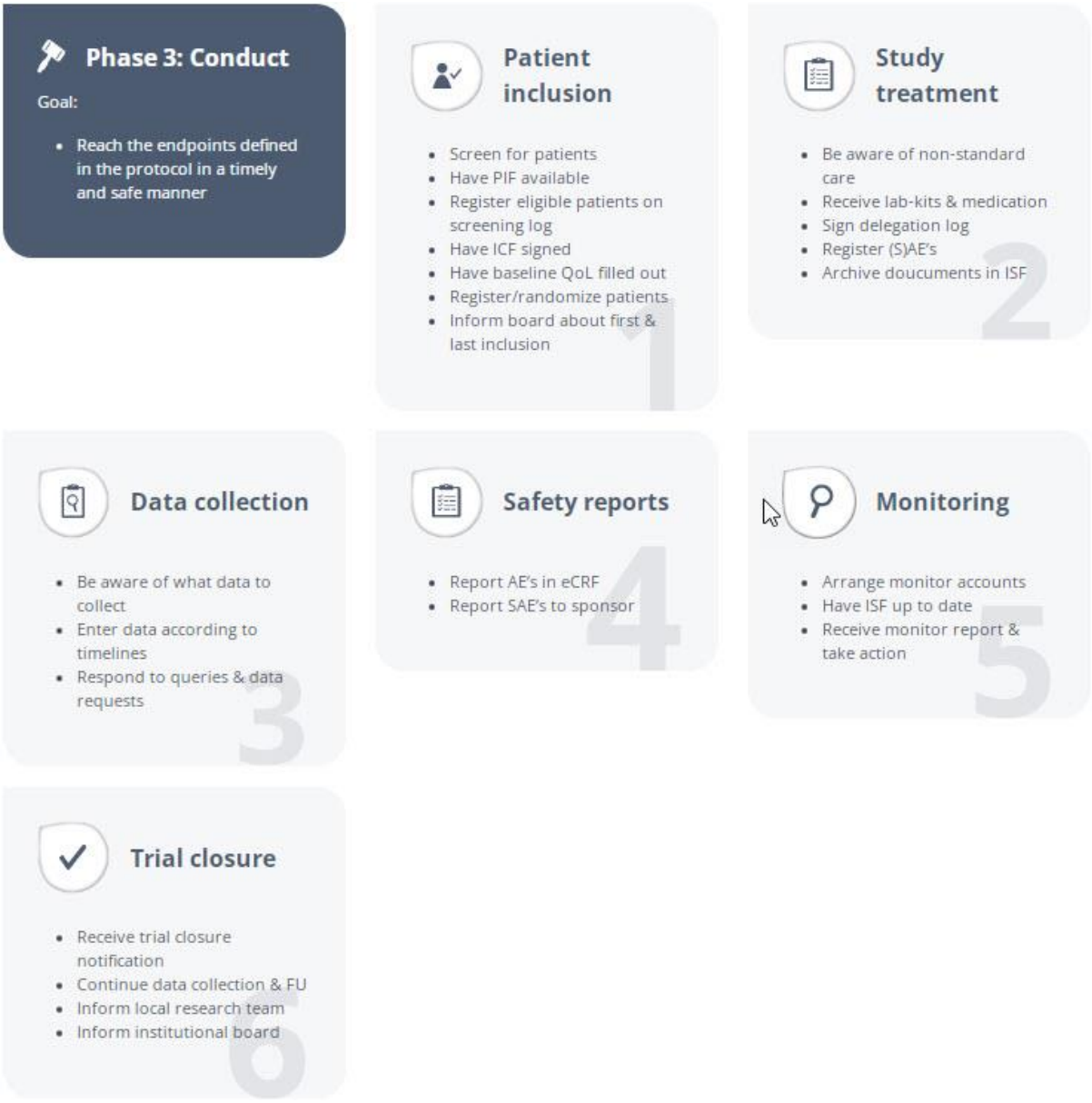
During the MEC review procedure:
- The sponsor provides an ISF (Investigator Site File) to file all essential documents.
- The sponsor provides the delegation log. Fill out and archive the delegation log in the ISF. Send a copy to the sponsor upon request.
- The sponsor plans an initiation visit at which at least the local PI, research nurse, local datamanager and representatives from involved departments should be present.
- The sponsor provides accounts for registration/ randomization of patients and for access to the eCRF and guidelines.
- Finalize logistics.
- Finalize budget.
- Sign contracts: check and sign the CTA and return a copy to the sponsor.
- The sponsor provides working documents (for example pharmacy manual). Share these with involved departments.

2.4 Initiation

- After central MEC and local Institutional Board approval the initiation visit can take place.
- Organized by the sponsor.

- Invite involved departments and colleagues. Request all involved departments to be represented.
- Have the initiation log signed by all participants.
- Receive 'zakkaartjes' if available.
- Receive instructions how to inform patients. Providing information via different channels (spoken, written, online) and at different moments can increase willingness of patients to participate.
- Receive instructions about patient inclusion and how to register and/ or randomize patients. Patients cannot be withdrawn once randomized. Avoid erroneous inclusion as this effects the trial analysis. Receive instructions what to do in case of mistake (for example contact study coordinator)
- Be informed about non-standard or extra care (extra blood or tissue samples, special tubes, scans, extra information to note in the EPF). Protocol deviations will make the data unevaluable. When in doubt consult the PI or study coordinator.
- Receive lab-kits, medication, etc. in time. Check if the local stock is replenished in time.
- Receive instructions for taking, processing, sending or storing of (tumor) material.
- Receive working documents to instruct involved departments (pharmacy, radiotherapy).
- Receive instructions on how to handle baseline QoL.
- Be informed about what data will be collected in the eCRF to make sure all data is available in the EPF for source verification.
- Receive timelines for data entry. Timelines are maintained by CDM if involved, otherwise by a dedicated person from the coordinating center.
- Receive instructions how to handle (S)AEs. Because of timely SAE reporting it should be clear from the EPF if a patient takes part in a clinical trial (see also Phase 3: Safety reports, AEs, SAEs, SUSARs, SADEs).
- The following needs to be arranged before the site receives the start e-mail:
  -Local board and central MEC approval
  -CTA is signed
  -Delegation log is signed
  -Accounts (registration/randomization/eCRF) are arranged
  -Protocol signature page is signed
  -PIF is site-specific (provided by the sponsor)
  -Initiation visit has taken place and initiation log is signed
- Once the start e-mail is received, the site is allowed to inform and include patients.

3 Phase 3: Conduct



3.1 Patient inclusion

- Use 'zakkaartjes' if made available by the sponsor.
- Patients can only be informed about the trial after the site is initiated and received the start e-mail.
- Screen for patients that fulfill the in- and exclusion criteria of the trial.
- Inform colleagues about the trial and ask them to be aware of patients that fulfill the in- and exclusion criteria. Ask them to refer patients that may be eligible. Or register colleagues on the delegation log to enable them to inform patients themselves.

- Introduce the trial at the MDO and be aware at the MDO of eligible patients from colleagues.
- If possible try to arrange that the trial pops up in the EPF for potential candidates.
- Instruct colleagues registered on the delegation log on how to inform patients about the trial. Providing information via different channels (spoken, written, online) and at different moments can increase willingness of patients to participate. Have patients (also) informed by someone with whom there is a relationship of trust, such as their practitioner or research nurse.
- Have patient information readily available to inform patients about the trial.
- Give patients sufficient time to read and understand the PIF. Be available to answer questions or make an appointment to discuss questions.
- Make sure the patient understands what it means to take part in a trial. The patient must be able to comply to the treatment including QoL.
- Confirm the patient is eligible and fulfills the in- and exclusion criteria before registering and/ or randomizing a patient. Patients cannot be withdrawn once randomized. Avoid erroneous inclusion as this effects the trial analysis. In case of mistake, inform your contact person and ask for instructions.
- Register eligible patients on the trial screening log (regardless of whether they are willing to participate) to be able to monitor how many patients are eligible and informed about the trial and how many finally participate.
- Register in the EPF if a patient decides to take part in the trial.
- Have ICF signed before any trial-related procedure (blood or tissue samples, questionnaires) is done.
- ICF is signed first by the patient and then by the local investigator. Sign the ICF in twofold or make a copy of the complete PIF + signed ICF. Give one copy to the patient, archive one copy of the PIF + signed ICF in the ISF.
- Have information to register and/or randomize the patient readily available. This can be a personal account login, contact info of the person(s) who is (are) delegated to register and/or randomize, or contact info (phone, e-mail) of the trial office appointed to register and/or randomize.
- Have baseline QoL filled out by the patient if applicable. Baseline needs to be filled out after signing ICF. Depending on the trial and according to instructions provided by the sponsor, baseline is before randomization or start treatment.
- Register/ randomize patient according to instructions provided by the sponsor.
- Inform the patient about the treatment arm if allowed and applicable.
- Send appointment reminders to patients to prevent drop-out.
- Inform the institutional board when the first patient is included.
- Inform the institutional board when the last patient is included (the study and FU continue).

3.2 Study treatment

- Adhere to the protocol and make sure to understand it.

- Be aware of non-standard or extra care (extra blood or tissue samples, special tubes, scans, extra information to note in the EPF). Protocol deviations will make the data unevaluable. When in doubt consult the PI or study coordinator.
- Receive and store lab-kits, medication, etc. Make sure the local stock is replenished in time.
- Distribute working documents to participating departments (pharmacy, radiotherapy).
- Register and sign the delegation log for all people involved in te trial, also from participating departments, and in case of changes.
- Follow instructions for taking, processing, sending or storing of (tumor) material.
- Register per patient what material has been processed, send or stored.
- Register (S)AEs according to instructions provided in the protocol (see also Safety reports, AEs, SAEs, SUSARs, SADEs).
- Implement amended protocol and PIF versions directly when available.
- Archive (new) documents in the ISF: protocol, PIF, ICF, etc.
- Check if any amendment requires that patients should receive and sign a new version of the PIF, according to instructions of the sponsor. If so, register in the EPF the new information is discussed. Give one copy of the signed ICF to the patient, archive one copy in the ISF.

3.3 Data collection

- Collect data in the eCRF. Depending on what is agreed this should be delegated to dedicated local datamanagers, the local PI or the local study team. If applicable, arrange that local datamanagers have a place to work, receive an institute account login and have permission to access to the EPF of trial patients.
- Be aware of what data to collect in the eCRF and make sure everything is registered and available in the EPF for source verification.
- Enter data according to timelines stated in the protocol or to what is feasible and agreed upon with the sponsor .
- Respond to questions and requests from datamanagers so they can continue data entry.
- QoL questionnaires can be distributed on paper or electronically. Per patient these should be send out, returned and processed at fixed timepoints specified in the protocol. This can be outsourced to a dedicated organization. Check with the sponsor how this is organized for the trial.
- Respond to queries and data requests (if applicable via local datamanagers) and complete data collection.
- After the trial is closed for inclusion, follow up and data collection may continue. Check for how long and at what frequency. Plan follow up visits with patients.

3.4 Safety reports: AEs, SAEs, SUSARs, SADEs

- Report AEs in the eCRF. In the protocol it is defined which AEs should be reported. Register AEs in the EPF for source verification.
- Report SAEs and SADEs to the sponsor according to instructions.
- If in doubt contact the sponsor/ PI/ study coordinator.

3.5 Monitoring

- The monitor plans visits according to the monitor plan, depending on onsite and centralized/remote monitoring.
- Arrange monitor accounts if requested. Permission for monitors to access the EPF is agreed upon in the CTA.
- Have ISF up to date. The monitor checks if all versions of protocol and PIF, delegation log, signed ICF for all patients, etc. are archived.
- The monitor checks for patients' rights, wellbeing and safety.
- The monitor checks whether data is correct, complete and verifiable to source documents.
- The monitor checks whether the conduct of the trial is in accordance with the current version of the protocol.
- Receive the monitor visit report and take action if needed. The monitor communicates the report to the involved site and the sponsor.

3.6 Trial closure

- Receive a notification of the sponsor that the trial is closed for inclusion.
- Continue data collection and follow up according to protocol and instructions from the sponsor.
- Inform the local research team and departments involved.
- Inform the Institutional Board that the trial is closed for inclusion.
- Receive a notification of the sponsor that data collection and follow up are closed.
- Inform the local research team and departments involved.
- Inform the Institutional Board that the trial is closed for follow up.

4 Phase 4: Analysis & publication

4.1 Manuscript preparation & publication

- Publications will be joint publications with the participating centers. Since the number of co-authors may be restricted by the journal, publication as a group has to be considered by the sponsor. Check what is agreed on in the CTA.
- Review the manuscript if requested by the sponsor.
- Inform included patients about the results and where follow-up results can be found. A letter to the patients is provided by the sponsor.
- The sponsor writes a layman's summary and uploads this in CTIS within one year after trial closure. This is obliged to comply with the CTR.

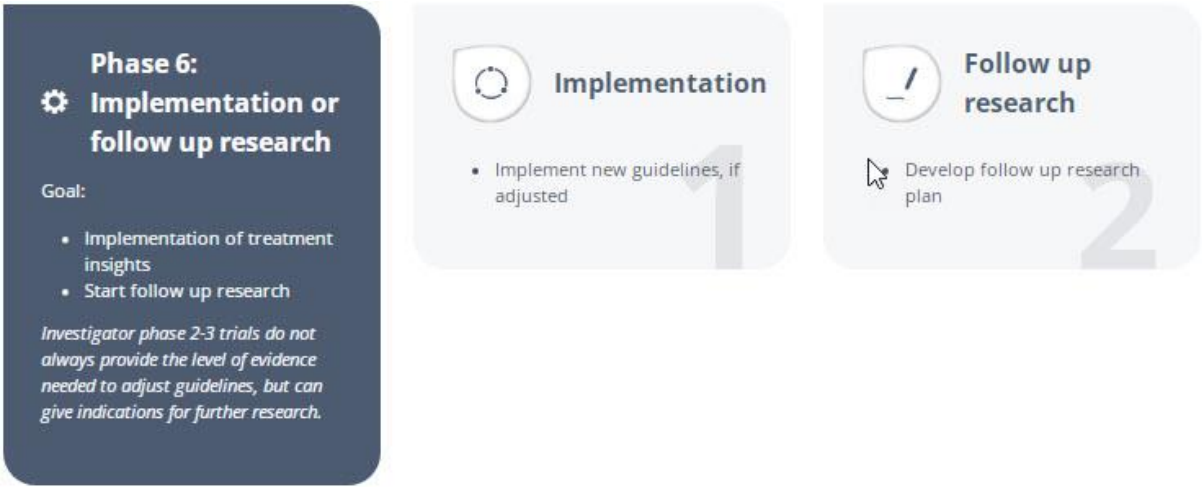
5 Phase 5: Wrap up

5.1 Archiving

- Archive eCRF according to sponsor instructions.
- Archive QoL questionnaires according to sponsor instructions.
- Archive ISF according to law and regulations after the study is closed, commencing after the last visit (or research related activity) from the last patient worldwide. Directly traceable data must be stored separately from the encoded data.
- Archive patient material (locally or in biobank) according to predetermined retention period, requirements and instructions of the sponsor.

6 Phase 6: Implementation or follow up research

Investigator initiated phase II/III trials do not always provide the level of evidence needed to adjust guidelines, but can give indications for further research. The following steps are optional and depend on the trial results.



6.1 Implementation

- Implement new guidelines, if adjusted.
- Bring new guidelines to the attention of colleagues.

6.2 Follow up research

- Develop follow up research plan, see Phase 1.

7 List of abbreviations

BROK	Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers
CCMO	Competent Authority (Centrale Commissie Mensgebonden Onderzoek)
CDM	Central Datamanagement
CRO	Clinical Research Organisation
CTA	Clinical Trial Agreement
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
DTA	Data Transfer Agreement
(e)CRF	electronic Case Report Form
EMA	European Medicines Agency
EPF	Electronic Patient File (=EPD)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IC	Informed Consent
ISF	Investigator Site File
LDM	Local Datamanagement
LPLV	Last Patient Last Visit
MDO	Multidisciplinairy consultation (Multidisciplinair overleg)
MEC	Medical Ethics Committee
MTA	Material Transfer Agreement
NKR	Nederlandse Kanker Registratie
NTR	Netherlands Trial Register
OMS	Organization Management System
OV	Onderzoeksverklaring
PI	Principal Investigator
PIF	Patient Information Folder
QoL	Quality of Life
RFI	Request For Information
SAP	Statistical Analysis Plan
TMF	Trial Master File
WMO	Wet Medisch-wetenschappelijk Onderzoek met mensen