Partnering with a Clinical Trial Unit: Key to a successful trial

Information for potential Chief Investigators

NCRI
National Cancer
Research Institute
Cancer CTU Group

Summary

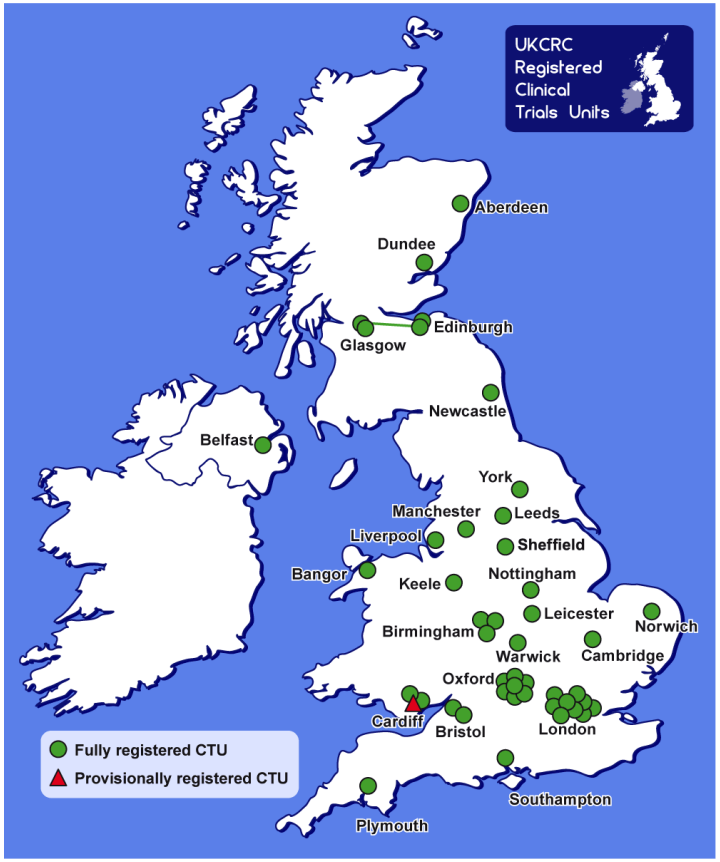
- What is a CTU?
- What does a CTU do / not do?
- Why work with a CTU?
  - What are the benefits of partnering with a CTU?
- When to engage with a CTU
- What to expect from the CI role

CTU = Clinical Trial Unit

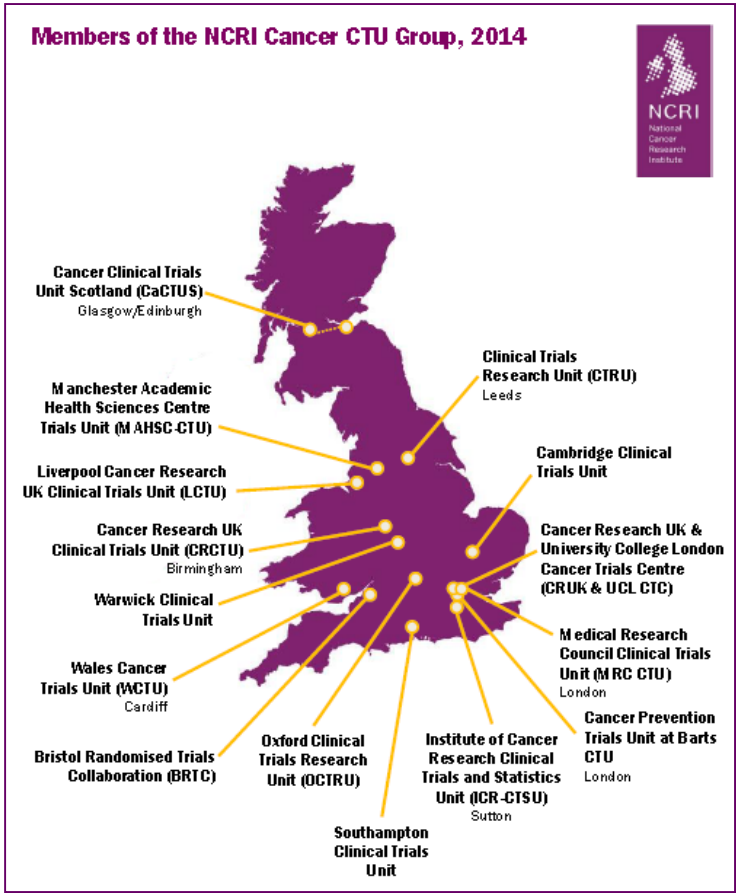
CI = Chief Investigator

What is a CTU?

UK Clinical Trials Units (CTUs) Infrastucture



47 National UK Clinical Research Collaboration Registered CTU's



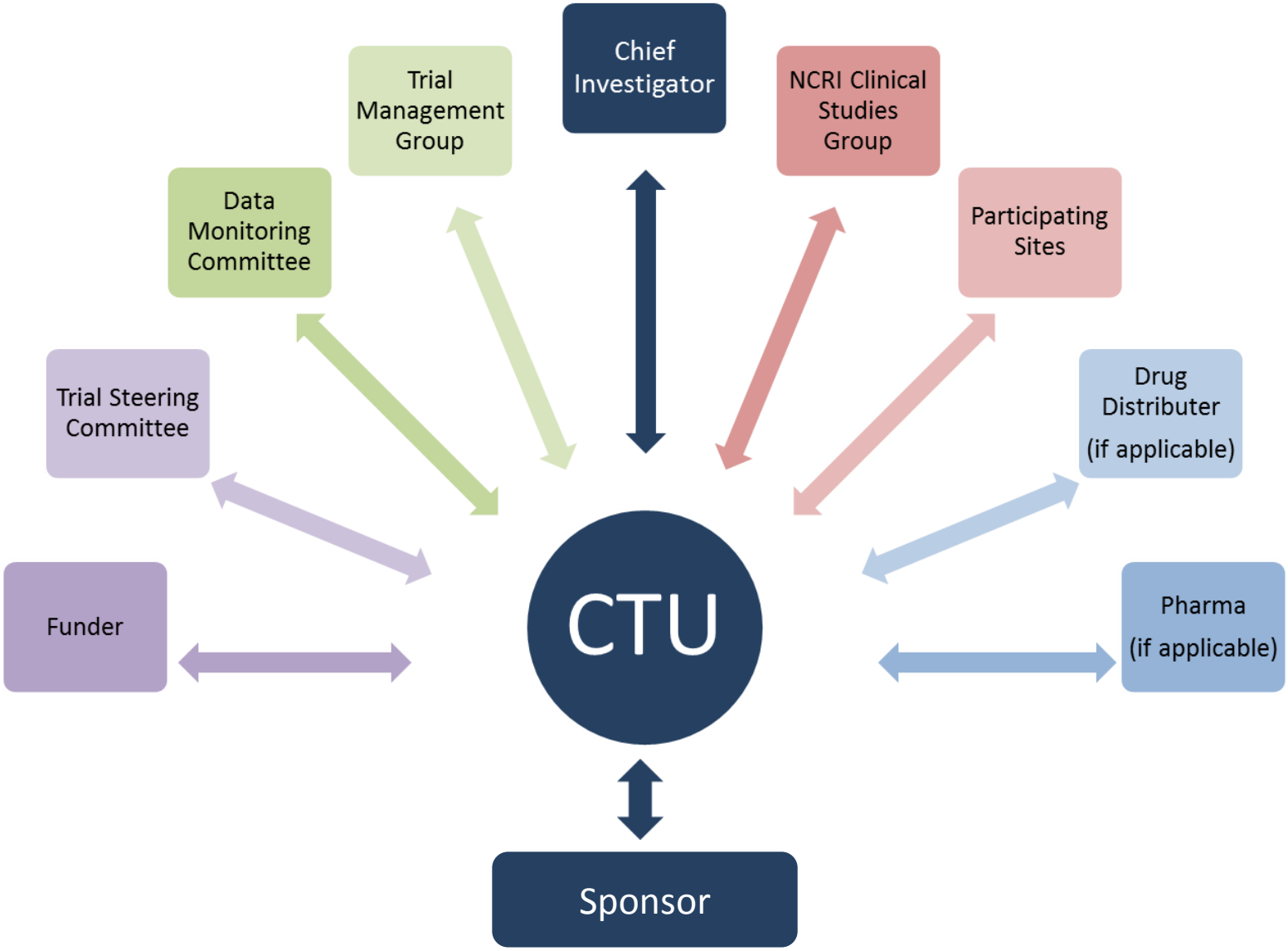
15 members of NCRI Cancer CTU Group

UKCRC CTU Registration

- **Full registration** – key core competencies
  - Track record of coordinating multi-centre Randomised Controlled Trials (phase II-IV) or other well-designed studies
  - Presence of core team
    - expert staff to develop and support studies
  - Presence of robust quality assurance systems and processes
    - to meet appropriate regulations and legislation
  - Evidence of longer-term viability
    - capacity for trials coordination
    - development/maintenance of a trials portfolio
    - core funding or evidence of a rolling programme of grants
    - evidence of commitment from the host institution

- **Provisional registration**
  - have recognised expertise
  - working towards full registration

Key Relationships



What do CTUs do?

Concept

- Advise on trial concept and trial design
- Review available literature to inform sample size calculations
- Conduct feasibility assessments
- Manage completion of grant application
- Calculate research costs

Set-up

- Develop all trial materials incl. protocol and PIS
- Conduct risk assessment
- Obtain regulatory, ethics and global NHS permissions
- Ensure appropriate sponsorship arrangements
- Oversee contract negotiations and development
- Ensure appropriate arrangements for treatment allocation and labelling & distribution of trial drugs
- Develop trial materials & guidance notes for investigator & pharmacy files
- Ensure appropriate arrangements for sample collection and tracking
- Develop plans for data management, central and on-site data monitoring and statistical analysis
- Develop CRFs & trial database
- Develop databases to track and monitor data & sample flow

Conduct

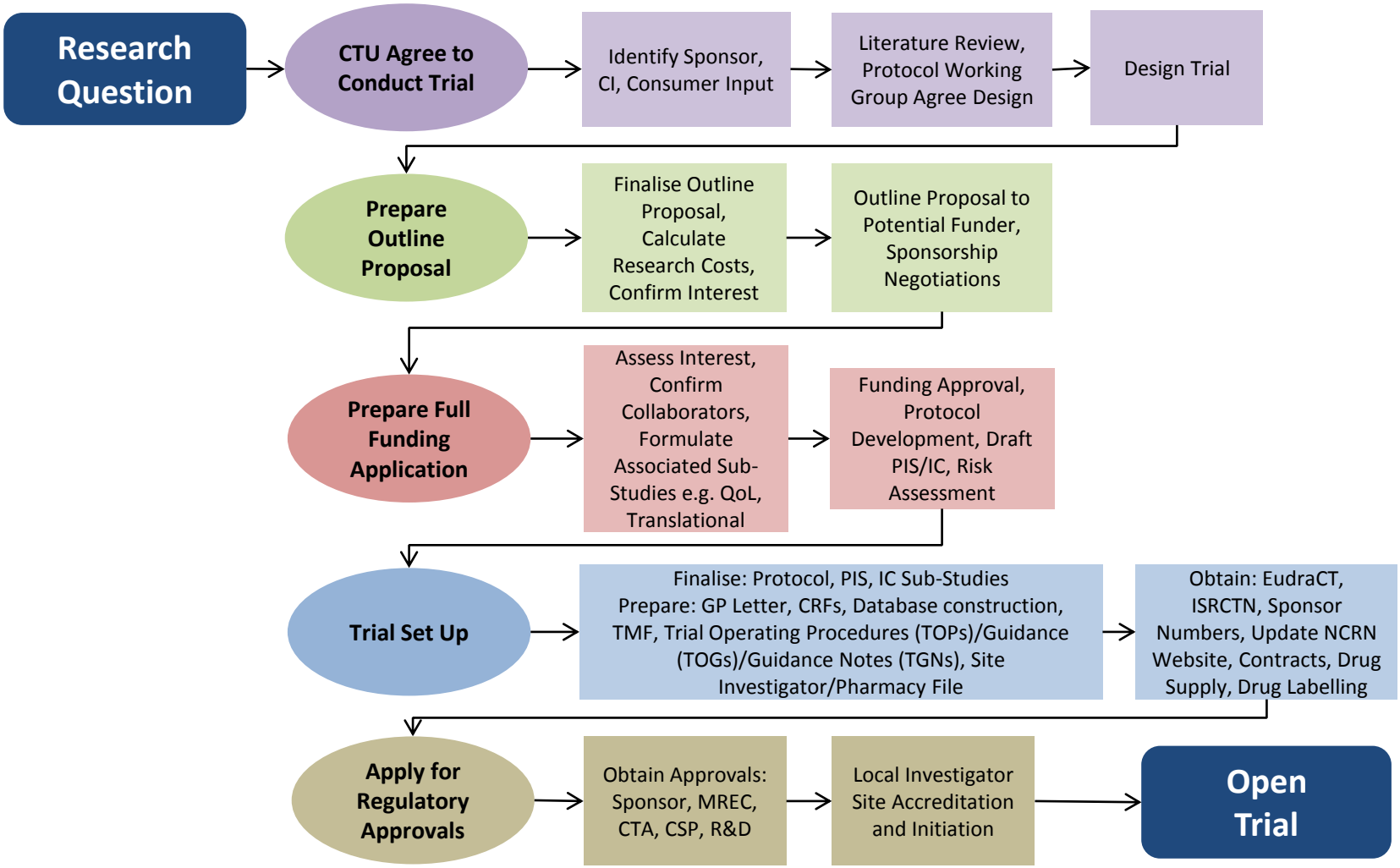
- Organise launch meetings & conduct initiations of participating sites
- Provide a randomisation service
- Provide on-going oversight & advice to participating sites
- Monitor & administer site payments
- Centrally collate and enter data
- Review data for completeness & accuracy - chasing data & querying where necessary
- Conduct central and on-site monitoring
- Develop newsletters & promotes the trial
- Help Identify & address barriers to timely recruitment and conduct
- Manage pharmacovigilance activities in accordance with regulations
- Arrange, contribute to and administer Trial Management group (TMG) and Trial Steering Committee (TSC) meetings
- Maintain trial approvals
- Prepare reports for funders, regulators, sponsors etc
- Maintain essential documentation
- Facilitate audits & regulatory inspections

Analysis & Reporting

- Conduct statistical analyses according to pre-defined analysis plans
- Arrange, contribute to and administer Independent Data Monitoring Committee (IDMC) meetings
- Provide statistical reports for IDMC meetings
- Conduct additional exploratory analyses as agreed by the TMG
- Contribute significantly to drafting of manuscripts, abstracts and presentations
- Administer the submission of manuscripts, abstracts and presentations
- Present at (inter)national symposia as required

Funding Period

Trial Development Process

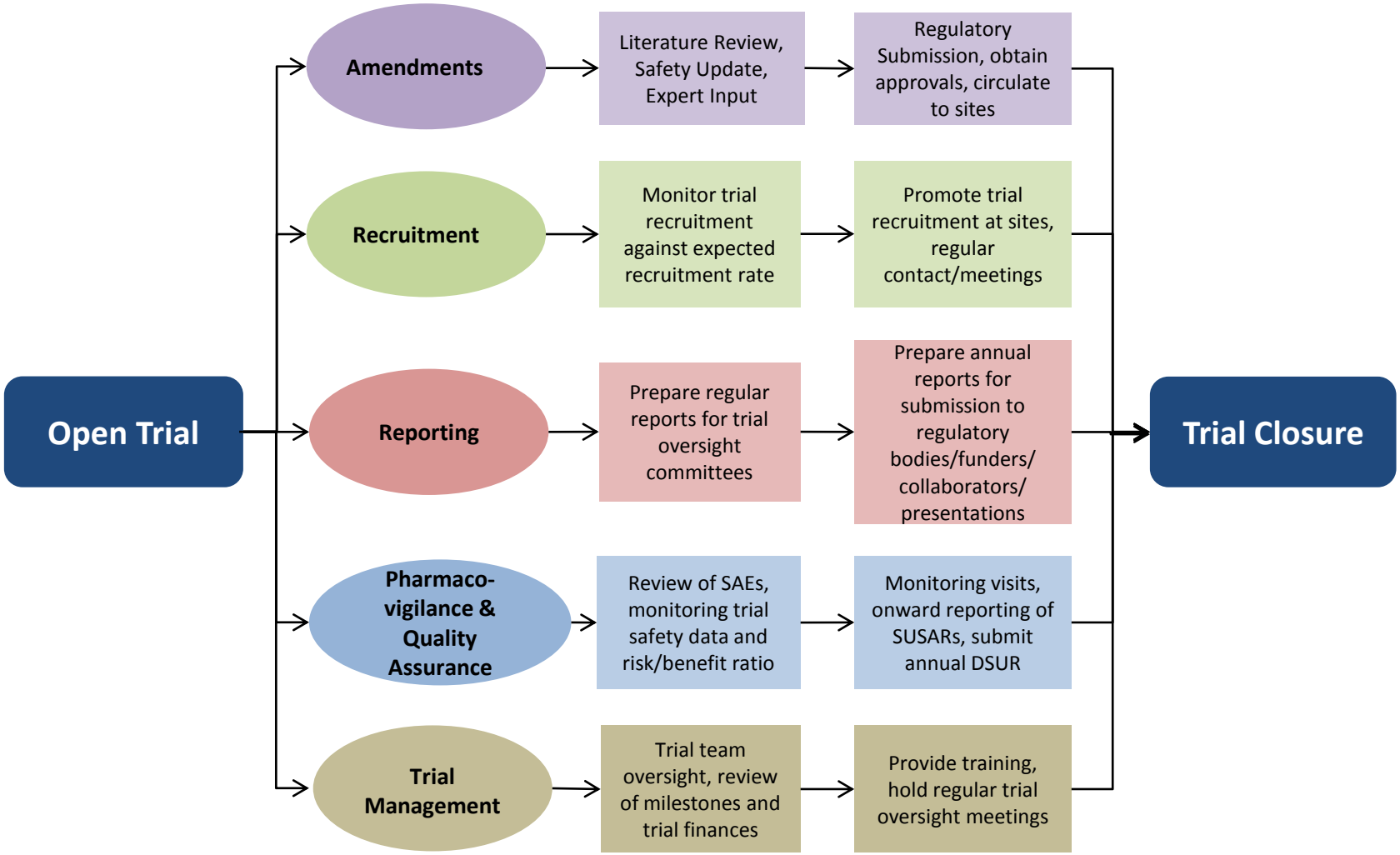


PIS = Patient Information Sheet
IC = Informed Consent

CRF = Case Report Form
TMF = Trial Master File

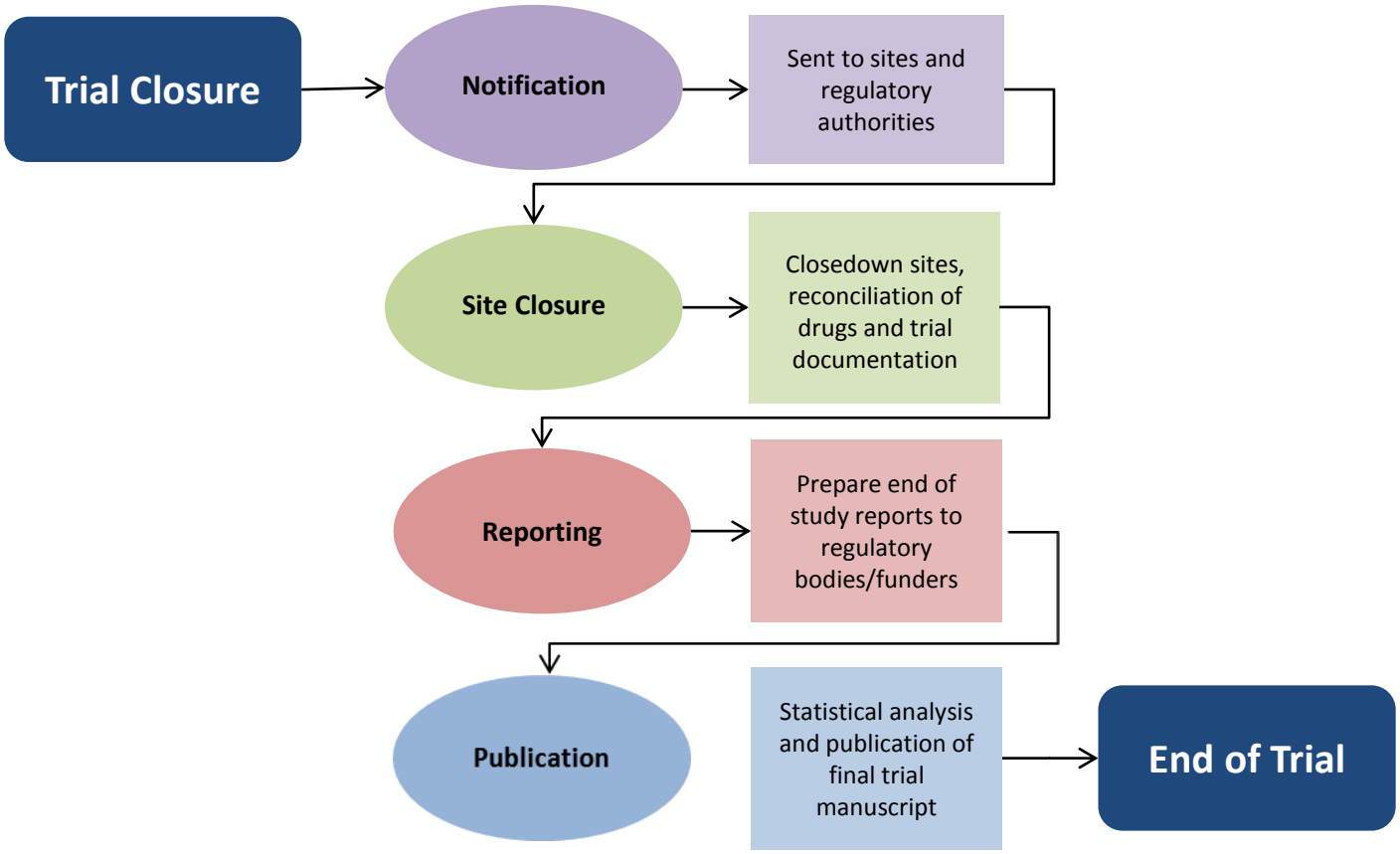
CT = Clinical Trial Application
CSP = Coordinated System for NHS Permissions

During the Trial



SAE = Serious adverse event
SUSAR = Suspected unexpected serious adverse reaction
DSUR = Development safety update report

End of the Trial



What CTU's don't do

- Interface with patients
  - Other than sending out patient reported outcome questionnaires eg quality of life

- Store, label dispatch IMP's, ATIMP's or biological samples
  - Although processes may be managed by CTU

IMP = Investigational Medicinal Product

ATIMP = Advanced Therapy Investigational Medicinal Product

Why Work with a Registered CTU?

- Grant success rate – some funders require it!
- Core infrastructure support - before grant funding
- Expertise
  - Trial design
  - Contract negotiation
  - Trial costing
  - Navigation through regulatory requirements
  - Risk assessment
  - Avoidance of preventable problems
- Ready made systems and procedures

Working with a CTU

"As a CI you are expected to have detailed knowledge of every part of the study and the CTU is critical in ensuring that every area is covered. The CTU is essential...one needs the expertise that is available, running all the way from the finances, planning, protocol writing and regulatory issues."

Daniel Hochhauser

Professor in Medical Oncology

UCL / UCLH

CI: PANTHER

Working with a CTU

"Working with the CTU helped me to turn my academic ideas into practical reality. Nothing was ever "no". It was always just about how long, how many, how often, how much etc. Instead of being another constraint, their pragmatic approach was, paradoxically, freeing."

Adele Fielding

Professor in Haematology

UCL / Royal Free Hospital

CI: UKALL 14 & UKALL 60+

Alternatives to working with a CTU?

- Research Design Service (RDS)
  - Help with trial design /sample size only
- Consider how you will manage
  - Ongoing statistical support /analysis
  - Sponsorship
  - Contracts negotiation and sign off
  - Regulatory support etc
  - Database creation and management
  - Staffing including training & supervision needs
  - Initiation, monitoring, safety reporting
  - Patient and public involvement

Benefits of working with a CTU

Funding Success

- CTU's have proven track record
  - Know what a fundable application looks like
  - 25% of HTA & CR UK grants are funded
  - 74% of CTAAC grants applications funded when NCRN CTU partnered application*
- CTU's are familiar with
  - trial costings
  - risk assessment
- CTU's assist with completing the application

***UKCRC CTU Oversight Group Review of CTU Capacity - Nov 2008**

HTA = Health Technology Assessment

CTAAC = Cancer Research UK's grant awarding committee until 2015

The view of the Funding Committees

"It's very clear when high quality funding applications have been developed in collaboration with a CTU. Even proposals of scientific merit risk being turned down if the trial conduct, costings and trial design are not well presented. "

David Sebag-Montefiore

Professor in Clinical Oncology

St James's Institute of Oncology, Leeds

CI: ARISTOTLE & CR07

Former Chair CR UK CTAAC

The view of the Funding Committees

What makes you look favourably on an application?

"Even though the applicant may be new, it's important that the group who they collaborate with has a good track-record and are experienced. Similarly, it is important to gain help from a clinical trials unit that is experienced in running such trials."

Mark Saunders

Consultant Clinical Oncologist

Christie Hospital Manchester

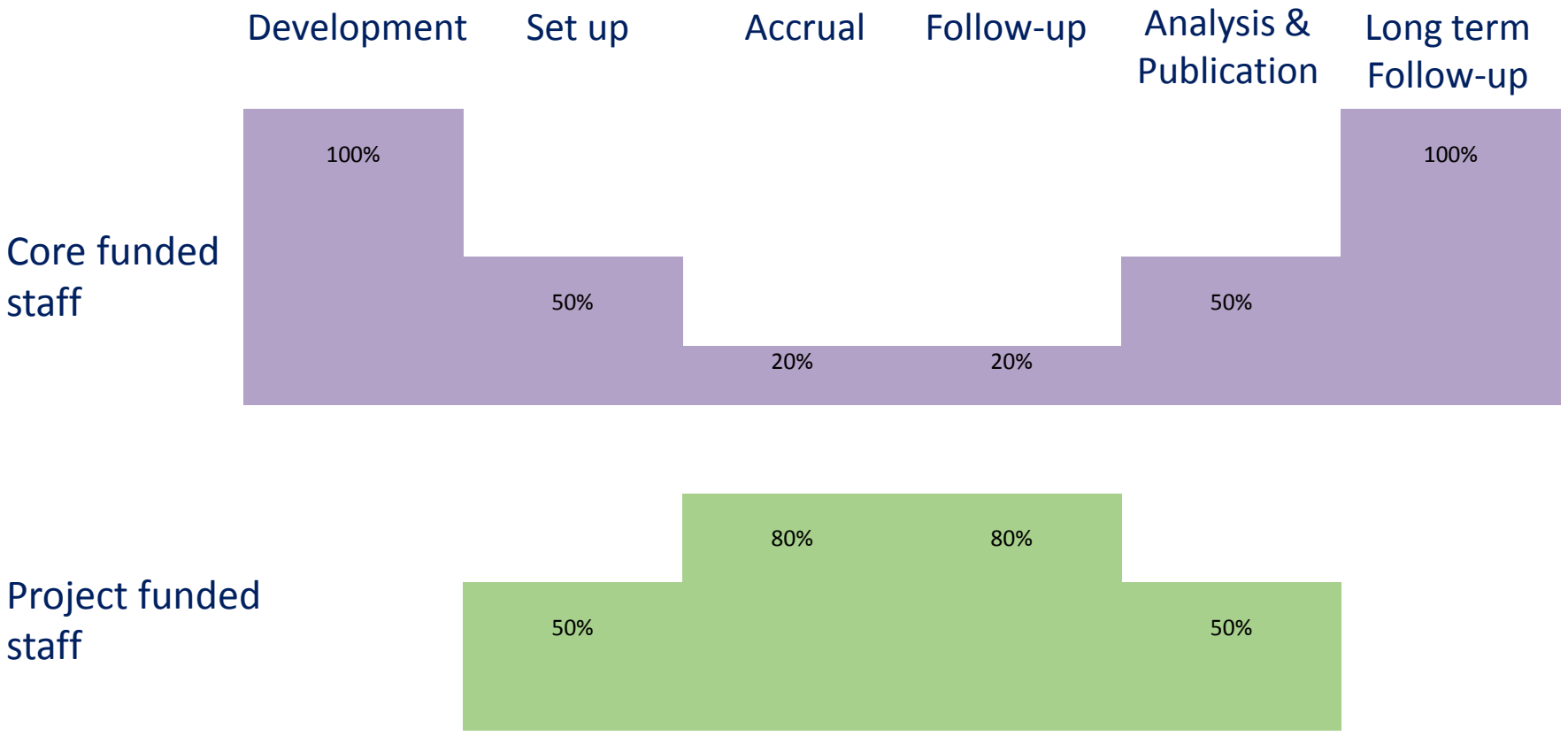
Former CR UK CTAAC member

Access to CTU Infrastructure

Why is this important?

- Trial lifespan longer than duration of the grant
- Non-grant funded activity
  - eg contract negotiations
  - Specialist advice eg regulatory
- Staff training and continuity
- Accumulated knowledge and experience
  - eg problem solving/ troubleshooting

Contribution of Core and Project Funded Staff to Direct Trial-related Activities



UKCRC CTU Oversight Group Review of CTC Capacity - Nov 2008

- Core activity is essential in underpinning and enabling Project-specific activity and ensuring development and delivery of projects is maintained and is conducted to highest quality.
- Core activity not necessarily carried out by full time core staff. Often staff are partly funded through core and partly through project specific funding.

Appropriate Trial Costing

What impacts on cost?

- Risk of trial – monitoring requirements
- Phase of trial
- Duration
- Intervention
- Research costs to sites eg Trial specific assessments
- Number and location of sites eg International sites
- Sub studies eg
  - QoL
  - Sample collection
  - Central QC – pathology, imaging etc

Getting the funding right

"As an investigator you are keen to start ASAP, but sometimes its wise to delay an application for funding; that way you submit the best possible application and haven't missed the chance for funding by rushing. The CTU team advice makes your study better and more likely to be funded.

Maria Hawkins
Associate Professor and Honorary Consultant Clinical Oncologist
Oxford University Hospitals NHS Trust
CI: CHARIOt, SPARC & ABC07

Getting the funding right

"The CTU will provide important information on costing, including all the "hidden" costs that may not be obvious to the new CI. They will guide you through the (sometimes confusing) definitions of research vs treatment costs. If all costs are not considered and applied for then it could prevent a study from proceeding smoothly."

Charlotte Coles
Consultant Clinical Oncologist
Cambridge University Hospitals
NHS Foundation Trust
CI: IMPORT HIGH & LOW & PRIMETIME

Grant funding

- Why do CTU's vary?
  - Core support from funder may reduce cost
  - Institutional overheads

CTU Funding requirements

Why does it cost so much?

- Staffing (*FTE depending on trial complexity*)
  - Trial manager
  - Statistical support
  - Database construction
  - Data management
  - Regulatory and Quality Management

- Running expenses
  - Computer, software, etc
  - Administrative costs

Non-CTU costs

- Site costs
- Intervention
- IMP distribution
- Translational research

- Don’t ask for too little
  - Underfunding impacts on trial success
    - Understaffed
    - Patient safety at risk
    - May cause delays
    - **Unethical!**

CTU Director Quote

"Beyond having a good question it's important to **engage with a CTU from the outset** in order to ensure that all the vast regulatory and financial landscape can be addressed and to maximise the chances of successfully delivering the trial and obtaining a top quality answer to the question"

Professor Robert Jones
Professor of Clinical Cancer Research
Director: CR-UK Clinical Trials Unit
Beatson Oncology Centre Glasgow

CTU Director Quote

"The consequences of not involving a CTU in the early stages of negotiations with Pharma can lead to problems with underfunding and a lack of clarity on who is responsible for what eg. who owns the data, who can publish what. This can lead to major problems and delays"

Professor Jonathan Ledermann
Professor in Medical Oncology
Director: CR UK & UCL Cancer Trials Centre

Negotiating with Industry

How can a CTU help?

- Prior experience with a variety of companies
  - Understanding the pitfalls
- Requesting realistic funding
- Contract negotiation
  - Understanding the wider implications
- Investigational Medicinal Product management
  - What works

When to engage with a CTU?

- Right from the start!

- Why?
  - It’s not just about trial design
  - Contracts
  - Costings
  - Navigating the regulations

Working with a CTU at concept stage

"The worst case scenario of not working with a CTU from concept stage is that the study even if funded, is then undeliverable due to fundamental methodological flaws. A more common situation is that the trial design is suboptimal and it takes a huge amount of work to modify it. The CTU brings an enormous amount of expertise and are not just there for advice on the power calculation!"

Charlotte Coles
Consultant Clinical Oncologist
Cambridge University Hospitals
NHS Foundation Trust
CI: IMPORT HIGH & LOW & PRIMETIME

Working with a CTU at concept stage

"The aim of the CTU is to help you design and run the best study possible and CTU staff time is allocated to your study. Once they know what the trial is about they help you a lot with feasibility, funding, regulatory, statistics questionnaires etc.

Maria Hawkins
Associate Professor and Honorary Consultant Clinical Oncologist
Oxford University Hospitals NHS Trust
CI: CHARIOt, SPARC & ABC07

Engaging the right CTU

Factors to consider

- CTU Expertise and track record
  - Likely funder
  - Disease area
  - Intervention
  - Setting eg primary care, international etc
  - Methodology

- How to find out
  - Ask around
  - http://www.ukcrc-ctu.org.uk/

Engaging with CTU's

Key questions to ask a CTU

Will CTU collaborate if

- there is only one site?
- there are international sites?
- the trial is sponsored by Pharma?
- the trial is high risk?
- they haven't previously worked in disease area, setting etc?
- the trial is already funded?

What types of trials do CTU's take on?

- Depends on the CTU!

- CTU's are the best option if the trial
  - is multicentre
  - involves an Investigational Medicinal Product (AT/IMP)
  - is high risk
  - is in a disease, trial intervention / outcomes area in which the CTU already has expertise

CI vs PI
What's the difference?

- Principal Investigator: responsible for the conduct of the trial at their site

- Chief Investigator: responsible for the overall design, conduct (**at all sites**) and reporting

CI vs PI

"Taking on the role of a CI is a **significant** step up from PI....."

David Sebag-Montefiore,

Professor in Clinical Oncology

St James's Institute of Oncology, Leeds

CI: ARISTOTLE & CR07

CI vs PI
What's the difference?

Additional responsibilities

- Trial oversight / management of whole trial
- Protocol development and trial design
- Funding
- Trial Master File and all essential documents
- Data base validation and data management
- Regulatory submission and compliance
- Ethics submission
- Risk assessment / Safety / IMP Oversight
- Annual / End of trial Reports

CI vs PI : How different is it?

"I think its quite different. The role was primarily what I expected but there was much that I did not anticipate, particularly the amount of detail you must be aware of as the CI such as pharmacy, toxicities etc. You have to be really willing to take full responsibility."

Daniel Hochhauser,

Professor in Medical Oncology

UCL / UCLH

CI: PANTHER

Time Commitment for CI's

- **Prior to funding**
  - Very variable but start >3 month ahead of deadline
  - It can take over a year to determine the right design

- **Post funding**
  - Estimate 2-4 hours a week - very variable
  - Allow time to establish good working relationships
    - CTU staff
    - TMG
    - Site PI's
  - Availability for troubleshooting
    - Queries on eligibility, protocol, safety etc

Time Commitment – developing idea

"Its a time consuming process and it took a lot more time (to develop the protocol) than I had anticipated because of the company's strategy, emerging knowledge about PK and side effects."

Daniel Hochhauser,

Professor in Medical Oncology

UCL / UCLH

CI: PANTHER

Time Commitment : open trial

"I'm personally spending around 3- 4 hrs a week on issues relating to the study and that can be more or less on other weeks. We have regular 1hr fixed meetings every 2 weeks with the CTU."

Daniel Hochhauser,

Professor in Medical Oncology

UCL / UCLH

CI: PANTHER

Partnership working with a CTU

"Be prepared for regular meetings, inquisitive questions and suggestions. Listen, think and learn! Initially things can be a bit hard but working as a team becomes easier (and is sometimes fun)."

Maria Hawkins
Associate Professor and Honorary Consultant Clinical Oncologist
Oxford University Hospitals NHS Trust
CI: CHARIOt, SPARC & ABC07

Communication with CTU

"As a CI you will receive many e-mails from the CTU every month. You will need to be able to reply in a timely manner and prioritise your work accordingly. As the CI of ARISTOTLE (actively recruiting) I have a teleconference with the CTU every 3-4 weeks. "

David Sebag-Montefiore,

Professor in Clinical Oncology

St James's Institute of Oncology, Leeds

CI: ARISTOTLE & CR07

What should you expect from a CTU?

- **Trial Design and Funding applications**
  - Expertise in trial design and good track record in obtaining funding
- **Trial Expertise**
  - Support and guidance in preparing ethics applications
  - Protocols, case report forms and essential documents
  - Trial coordination, database development and data management
- **Communication and Reporting**
  - Kept informed of issues at sites
  - Preparation of trial reports for relevant committees and bodies
  - Preparation work for publications and presentations
- **Compliance**
  - Navigation through relevant clinical trial regulations and guidance
  - Best practice in clinical trial conduct from design to final publication
  - Risk management

What will a CTU expect from you?

The 4 C's

- **Collaboration**
  - Academic CTU's are partners not service providers
- **Communication**
  - Keep CTU in the communication loop eg messages for funder, R&D, REC's, MHRA, Investigators etc
- **Clinical input**
  - Timely input and review of clinical issues from protocol queries to safety reviews
- **Compliance**
  - Comply with CTU & Sponsor SOP's and policies to ensure compliance with appropriate clinical trial regulations, guidance and funder requirements eg formation of Trial Steering Committee's (TSC's)

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