Clinical Trials in Horizon 2020

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Clinical trials in H2020

- In the past:
  - No public funding for Clinical Trials until 2008-2009 (FP7)
  - It used to 'belong' to the pharma industry
  - The pharma industry used to set the research agenda
  - Resulted in unattended diseases and unexploited knowledge
  - The need for public funding emerged, via FP7/H2020:
    - Less structured in FP7
    - More structured in H2020

- In Horizon 2020:
  - Dedicated topics for clinical trials
  - Additional topics in which clinical trials are an option
  - US partners are welcome and can be funded

Clinical trials in H2020

Which clinical trials can be funded in Horizon 2020 ?

- Methodology:
  - Observational
  - Interventional
  - Randomized
  - Longitudinal
- Type of intervention
  - Medicinal products
  - Medical devices
  - Advanced therapies
  - Surgery
  - Education/Training
  - Psychotherapy
- Phases
  - ‘Phase 0’ to ‘Phase 4’

Must correspond to a specific topic

Clinical Trial basics

- Protocol driven
- Single center vs. multi-center
- Inclusion / Exclusion criteria
- Patient recruitment plan
  - Recruitment rate (no. of patients / month) – given or estimated
  - “Power analysis” to reach statistical significance
  - Expected no. of patients per site (medical center)
  - Flexibility in recruitment and overall duration
  - Drop outs and recruitment problems are always an issue

Clinical Trial basics

- Payments structure:
  - In industry-initiated, “Per patient” basis is common
  - Allows competitive recruitment
  - Profit might be included
- Many people are involved
- Clinical Trial monitoring is essential - CRO
- Data analysis
- Sponsorship and insurance

Clinical Research Organization

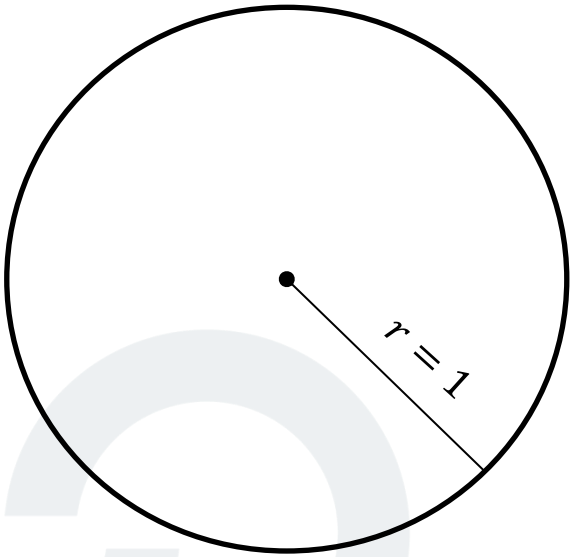
- Typical roles of CRO:
  - Patient recruitment management
  - Clinical Trial monitoring
  - Regulatory affairs / support (e.g. IRB, communication with competent authorities)
  - Data analysis and statistics
- Represent core expertise in managing Clinical Trials
- “For profit” companies and “Academic” CROs

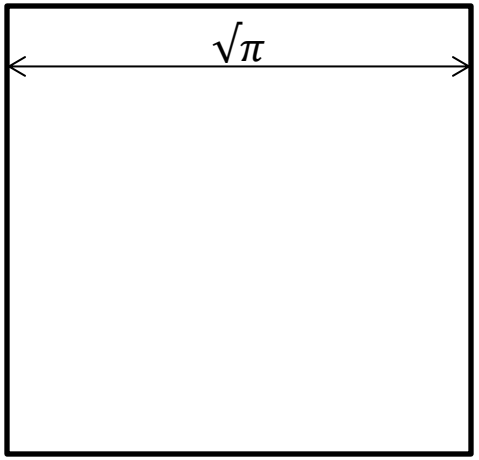
The H2020 RIA basics

- Clinical Trials are implemented in H2020 by the RIA instrument
- RIA (Research and Innovation Action) is one of the main H2020 funding instruments
- Addresses a specific topic in the H2020 Health work program
- Concrete deadlines
- Working in a consortium (minimum of 3 partner from 3 member states or associated countries)
- Can run for 3-5 years
- No flexibility in duration, once set
- Funding rate: 100% of all actual direct costs
- Overheads : 25% flat-rate on top of all actual direct costs (except for sub-contracting costs)
- Strict payment structure (in terms of timing and budget)

The challenge: Squaring the circle

- Inherent “conflicts”:
  - RIA template vs. Clinical Protocol structure
  - H2020 funding vs. Clinical trial payment structure
  - Fixed consortium structure vs. Competitive recruitment of patients
  - Typical and strict RIA duration vs. variable clinical trial timeframes
  - Legal and Ethical issues and conflicts
  - More…





Squaring the circle

RIA template vs. Typical Clinical Protocol structure

1. EXCELLENCE
- 1.1 Objectives
- 1.2 Relation to the work programme
- 1.3 Concept and approach
- 1.4 Ambition

2. IMPACT
- 2.1 Expected impacts
- 2.2 Measures to maximise impact
  - *a) Dissemination and exploitation of results*
  - *b) Communication activities*

3. IMPLEMENTATION
- 3.1 Work plan — Work packages, deliverables and milestones
- 3.2 Management structure and procedures
- 3.3 Consortium as a whole
- 3.4 Resources to be committed

Discrepancies:
Structure
Content
Length

LIST OF ABBREVIATIONS AND TERMS
1. BACKGROUND INFORMATION
1.1 Study Disease(s)
1.2 Name and description of the investigational product(s)
1.3 Study Rationale
1.4 Summary of the known and potential risks and benefits, if any, to human subjects
1.5 Rationale for dosage regimens and treatment scheme.
1.6 Description of the population to be studied.
1.7 A compliance statement with the protocol, GCP and the applicable regulatory requirement(s)
1.8 References
2. TRIAL OBJECTIVES
3. STUDY DESIGN
3.1 Overview of Study Design
3.2 Endpoints to be measured during the trial
3.3 Study Procedures
3.4 Accountability procedures
4. SELECTION AND WITHDRAWAL OF SUBJECTS
4.1 Inclusion criteria
4.2 Exclusion criteria
4.3 Subject Identification
4.4 Withdrawal criteria and procedures
5. STUDY RESTRICTIONS
5.1 Prior and Concomitant Medication
6. ASSESSMENT OF EFFICACY
6.1 Specification of the efficacy parameters.
7. ASSESSMENT OF SAFETY
7.1 Adverse Events
8. ADVERSE EVENTS
8.1 Definitions
8.2 Procedures for eliciting reports of and for recording and reporting AEs
8.3 Reporting of Serious Adverse Events
8.4 Definition of an Unexpected Adverse Event
8.5 SUSARs
8.6 Type and duration of the follow-up of subjects after occurrence of AEs
9. STATISTICAL CONSIDERATIONS
9.1 Study Design and Objectives
9.2 Endpoints
9.3 Sample size estimation

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Essential Information

- Respect the template!
  - Do not add information which is not requested (e.g. the full protocol)
  - Do not add chapters, annexes or change headings

- Identifier
- Study design and endpoints:
  - Study design
  - Primary and secondary endpoints, and how these are measured
  - Relevant guidance documents (e.g. guidelines from scientific societies, Health Technology Assessment agencies or regulatory bodies)
  - Scientific advice / protocol assistance / communication with regulatory / competent authorities / ethics committees
    - Full text answer / comprehensive summary of communication with the authority (e.g. EMA). Clearly define the regulatory / ethical status and requirements for the study according to the national and EU regulations

Essential Information

- Subjects / Population
  - Inclusion and exclusion criteria. Discuss inclusion of women and special populations.
  - Define sub-populations if subgroup analysis is planned
- Statistic analysis planning and power calculation – get your CRO involved here!
- Cumulative safety and efficacy information
  - Pre-clinical data from in-vitro or in-vivo studies; data from previous clinical studies; data from (pharmaco-)vigilance systems
  - Safety and tolerability of study interventions as well as efficacy of study interventions
- Conduct:
  - Schedule for study conduct including timelines for key study milestones
  - Description of recruitment strategy – realistic recruitment rate (subjects per month/per centre)
  - Assignment of intervention for controlled trial (randomization, blinding)
  - Study management, study monitoring, data and sample management, AE reporting etc.
  - Sponsor, coordinating centre(s) and committees
  - Study medication
  - Clinical centres
- Orphan Designation, if relevant to topic/proposal
- 'Unit cost' per patient break-down, if relevant

Mandatory Deliverables

- Note the following mandatory deliverables to be implemented in section 3 of the proposal:
  - First study subject approvals package
  - All approvals package (for clinical studies including more than one study site)
  - Midterm recruitment report
  - Report on status of posting results

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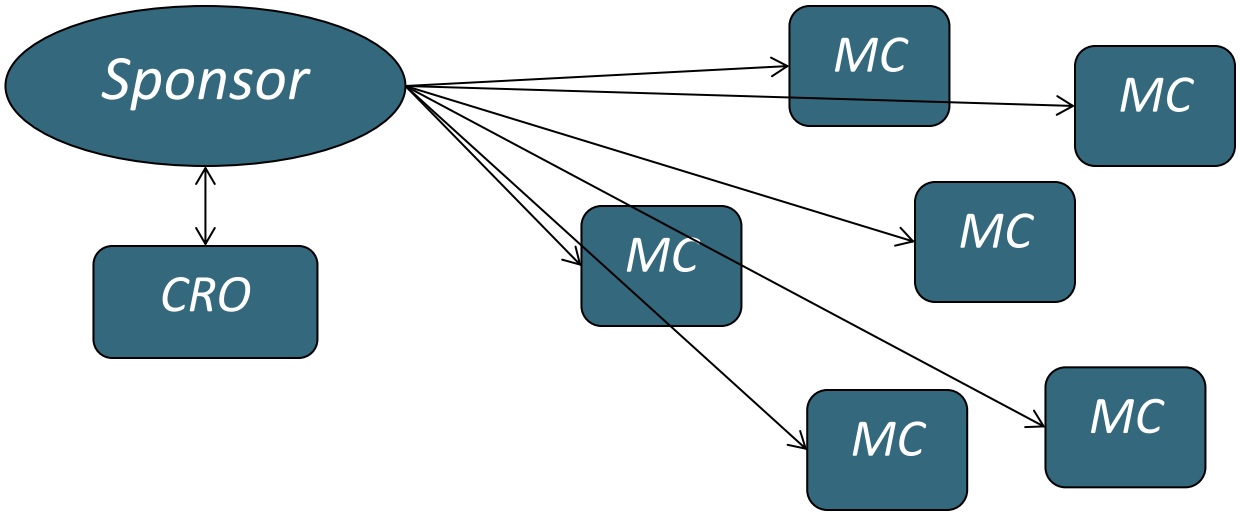
H2020 funding vs. Clinical Trial payment structure

A typical Clinical Trial:



- Medical Centers can be pre-defined or recruited Ad-Hoc
- Competitive recruitment of patients
- Pay per patient = Ongoing payment

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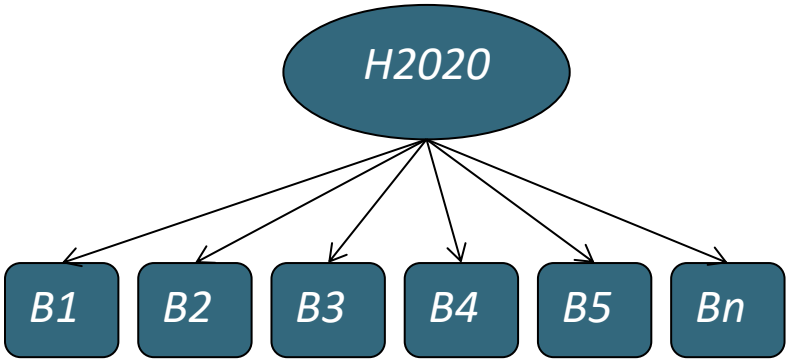
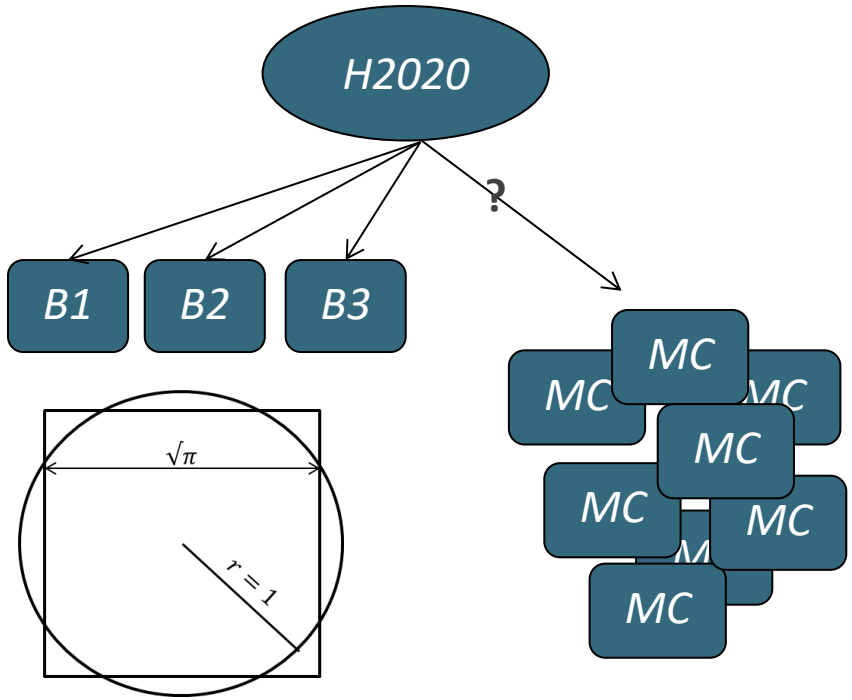
H2020 funding vs. Clinical Trial payment structure

In H2020:

- Each beneficiary is paid once in each reporting period (12 or 18 months)
- 2-4 payments/periods throughout the project



Clinical trial in H2020



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H2020 funding vs. Clinical Trial payment structure

The motivation: Pay Per Patient

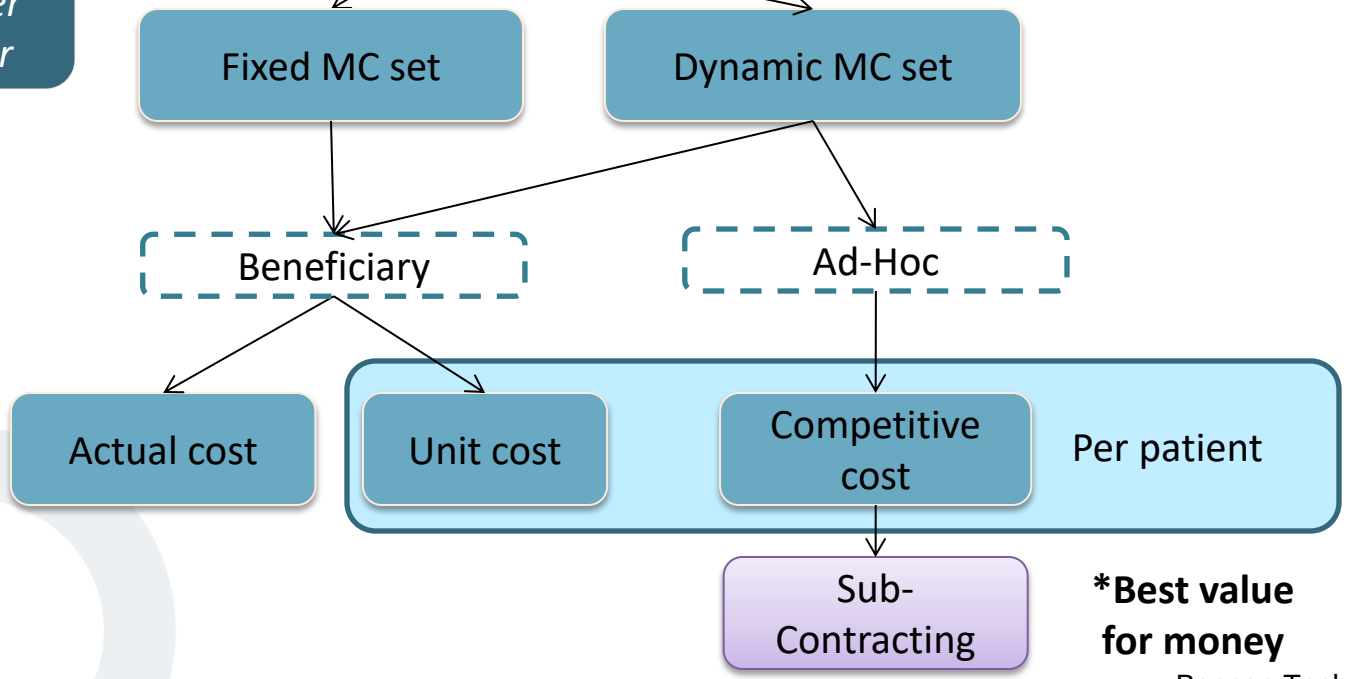
Sample size

=

Anticipated Recruitment per Medical Center

Number of Medical Centers

Orchestrating the MC funding



***Best value for money**

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H2020 funding vs. Clinical Trial payment structure

- H2020 Unit cost ≠ Typical clinical trial per-patient payment

$$\text{H2020 Unit cost} = \{A1\} \times \{B1\} + \{A2\} \times \{B2\} + [\ldots] + \{An\} \times \{Bn\}$$

- {Ax} (item of reference) can be any of the following items, per patient participating in the trial:
  - Estimated number of hours of Personnel (Medical Doctors, Other medical personnel and Technical personnel)
  - Consumables
  - Medical equipment (based on depreciation cost)
  - Other specific services
- {Bx} is the historical cost of the item in each medical centre according to **last closed financial year** at the time of submission of the grant proposal
- The list of reference units {A} is identical to all beneficiaries per clinical trial
- Costs {B} are specific to each Medial center

The recent “Unit Cost” update

- Decision C(2016) 7553 from Nov 2016 allows more flexibility and clarity to the way Unit Costs are implemented in Clinical Trials.
  - The ability to combine different reimbursement methods (actual or unit costs) was enhanced.
  - All personnel, assigned to **horizontal tasks** (e.g. study monitoring or study coordination tasks), can be calculated as actual cost, unit cost or a combination of the two.
  - Personnel **directly assigned** to the clinical trial, should be calculated as either actual or unit costs, but not a combination of both.
  - In case of multiple clinical trials under a single project, it is possible to have **different sets of cost calculations, per trial, for each beneficiary**.
  - Unit Cost can now be **corrected and modified** during the project execution under certain conditions.

Unit cost – good or bad?

- Advantages:
  - Easier budget estimation per beneficiary
  - Resembles per-patient reimbursement as done in industry-initiated trials
  - Easier and well justified budget transfer between beneficiaries (in the case of recruitment difficulties)
  - No need to document actual costs, e.g. timesheet management
  - Audit is easier
- Disadvantages:
  - The N-1 problem
  - Lack of flexibility: {A} and {B} can be modified through **amendment** to the GA only in two cases, while not increasing the requested contribution:
    - Change in the clinical protocol
    - Errors in calculation

Sub-contracting in Clinical Trials

- Sub-contracting is known to be unwelcome in Horizon 2020
- The big exception is in Clinical Trials
- Sub-contracting in Clinical Trials is welcome for:
  - CROs
  - Clinical sites
- Best value for money must be proven
- It allows to include profit (common issue with CROs)

- Plan with care

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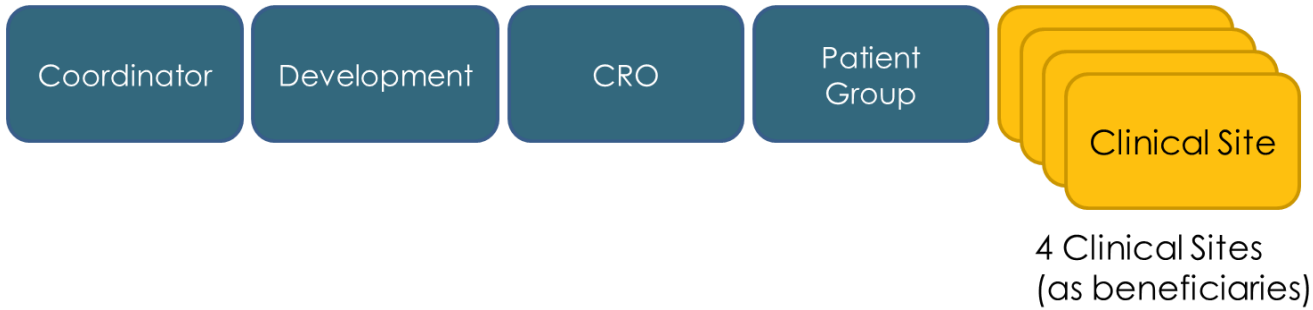
Fixed consortium structure vs. Competitive recruitment of patients

Fixed Medical Centers and consortium set :



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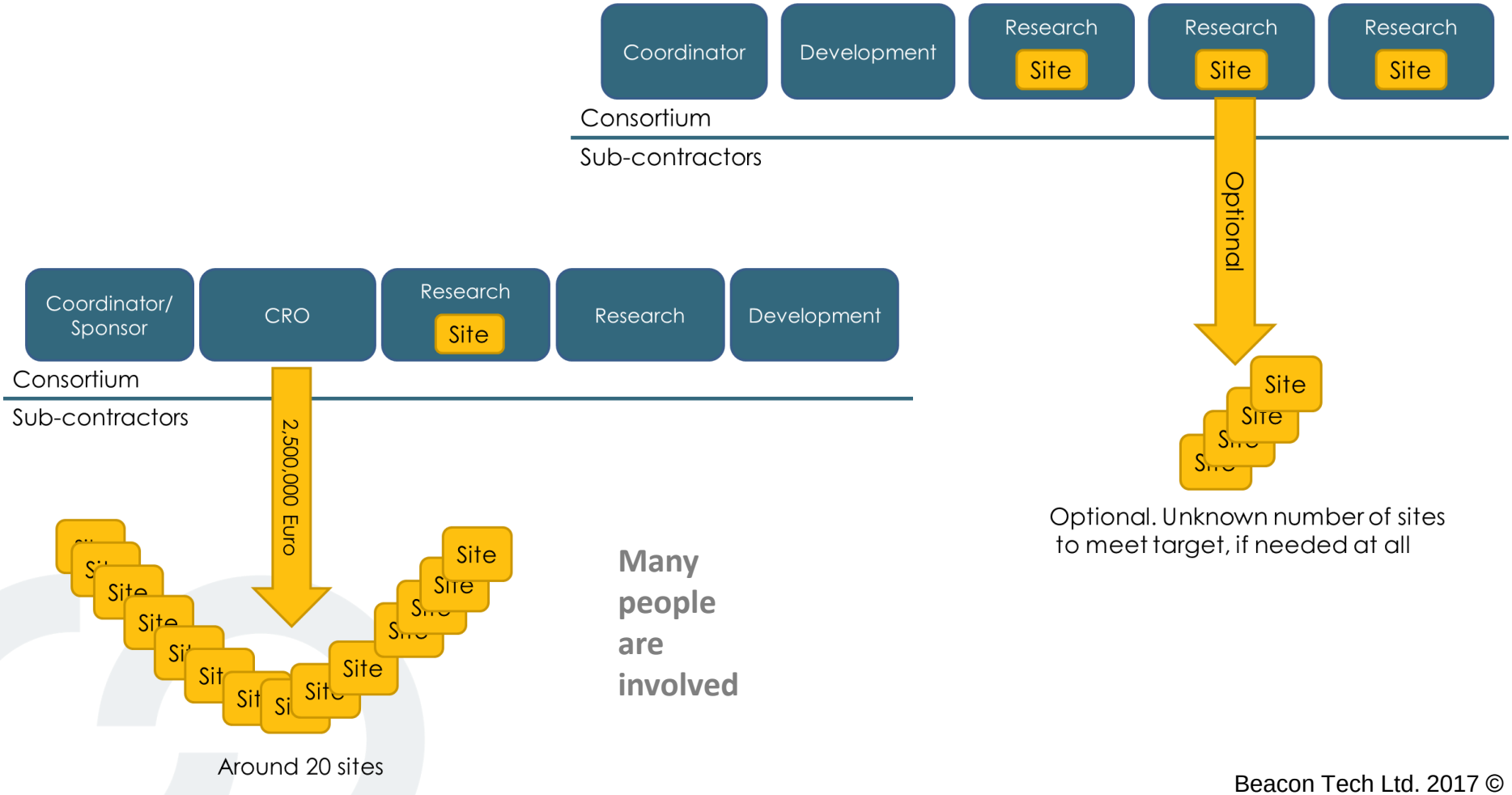
Fixed consortium structure vs.
Competitive recruitment of patients

Dynamic Medical Centers set :



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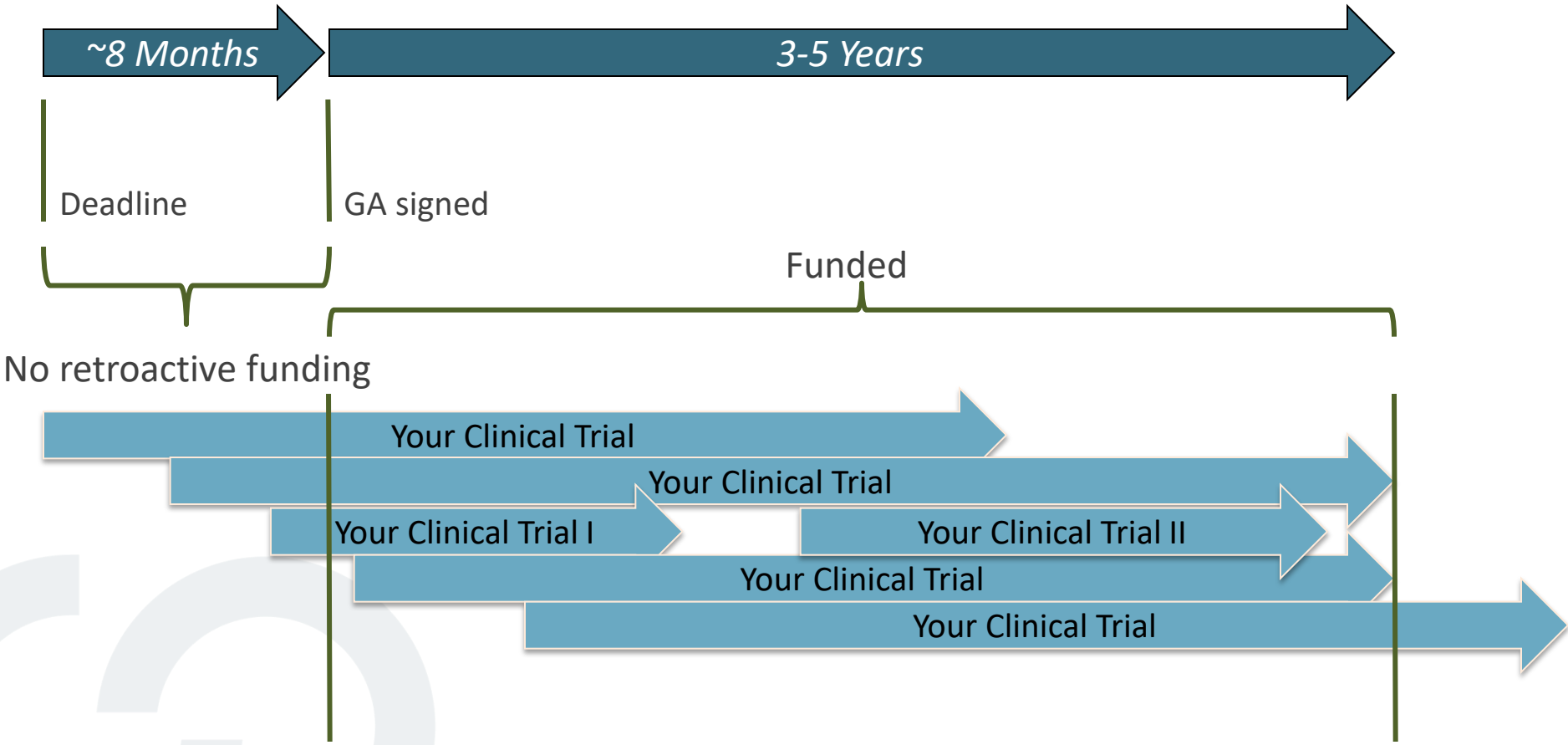
Typical and strict RIA duration vs.
variable clinical trial timeframes

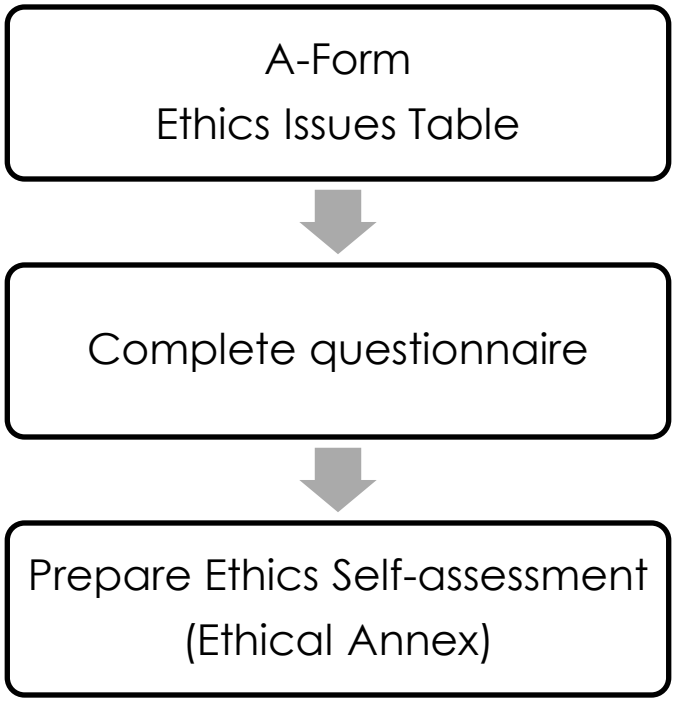


Legal and Ethical aspects

- The Clinical Trial must conform to the EU Clinical Trial Regulation No. 536/2014, Declaration of Helsinki and the principles enshrined in the Oviedo Bioethics Convention
- Potential issues to consider:
  - Liability (Insurance)
  - Non-EU sponsor
  - Regulation conflicts with the US (Indemnity)
- Ethical annex
  - IRB approvals – note call-specific requirements
  - Make sure no ethical issue was left unattended

Ethical Issues

- All proposals above threshold and considered for funding will undergo an Ethics Review
- The grant agreement cannot be signed until the review is complete and all conditions are met.
- Better be “Ethics ready”



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Ethical self-assessment – examples

Humans

- Which humans are involved?
  - vulnerable persons
  - persons unable to give consent
  - Children
- Are some interventions on the body foreseen?
  - invasive techniques (biopsy, EEG, fMRI)
  - Patients? Healthy volunteers?
- Which are the procedures for recruitment and consent?
- Documents to provide
  - ethics authorisations
  - information and consent forms

Data Protection

- Which data?
  - genetic data
  - sensitive data (health, political or religious opinions, sexual orientation, etc.)
- Which procedure?
  - procedure for collection – how, by whom, information on rights, info and consent forms, anonymisation
  - procedure for protection of data – how it is protected, encrypted, where, for how long?
- Documents to provide
  - data protection officer/authority authorisations
  - information and consent forms
  - security measures

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Ethical self-assessment – examples

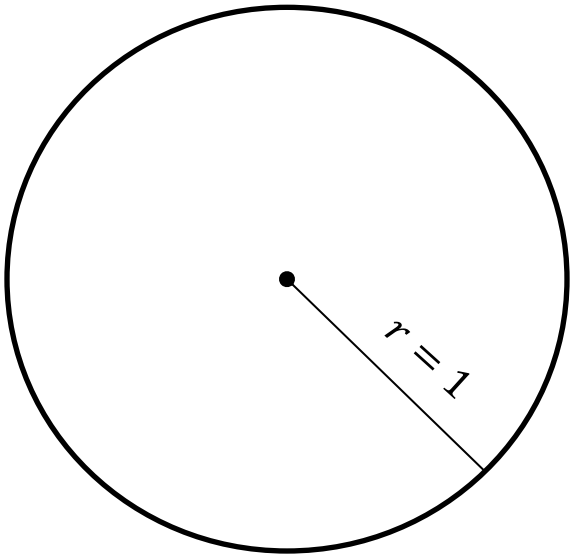
Cells and Tissues

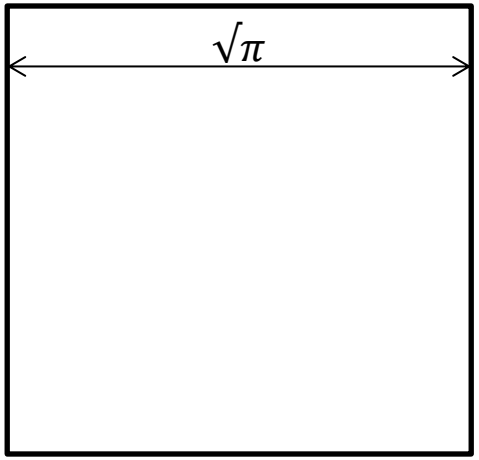
- What type?
  - hESCs
  - foetal cells/tissues
  - use or creation of cells/cells lines
- What for?
  - justification of use
  - origin: direct collection/ biobanks /secondary use
- Documents to provide
  - ethics authorisations
  - information and consent forms
  - justification of right for secondary use

Animals

- Which animals are involved?
  - vertebrates
  - GMOs
  - Primates
  - wild / protected animals
- For what use?
  - Justification for choice of species
  - 3Rs, precise evaluation of number
  - Description of procedure, husbandry, anaesthesia, euthanasia
  - Applicable legislation
- Documents to provide
  - Ethics authorisations / project license
  - personal and laboratory licenses

The main thing to remember:





Clinical trial topics – what to expect?

- Recurring topics:
  - Rare diseases
  - Chronic diseases
  - Regenerative medicine
  - Mental health
  - Infections diseases

European Medicines Agency - EMA

- The European Medicines Agency (EMA) is the European Union agency for the evaluation of medicinal products
- In calls addressing **rare diseases,** applicants typically need to show a granted orphan designation and might be asked to implement **recommendations from protocol assistance provided by EMA** in the clinical protocol.
- Orphan Drug designation applications are reviewed by the Committee for Orphan Medicinal Products (COMP)
- Protocol assistance is a form of scientific advice provided for development of orphan medicines by the Scientific Advice Working Party (SAWP)
- Both COMP and SAWP meet once a month, on predefined dates
- SAWP follows COMP, they are not parallel

European Medicines Agency - EMA

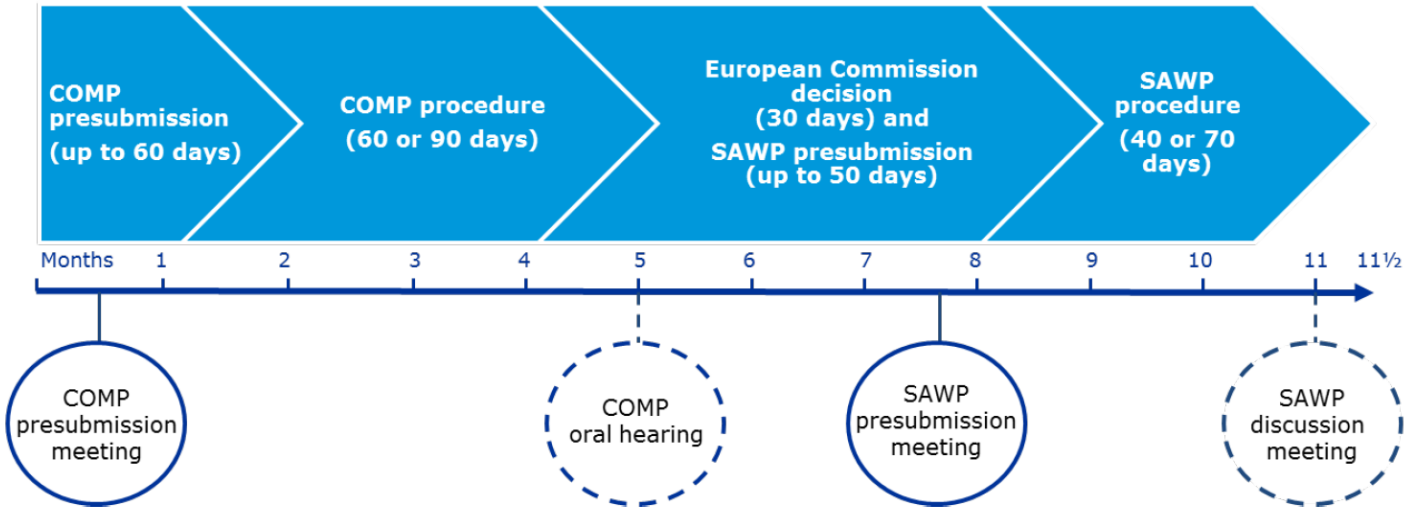
- To qualify for orphan designation, a medicine must meet the following criteria:
  - Targeting a disease that is life-threatening or chronically debilitating
  - Prevalence not more than **5 in 10,000 (rare disease)**
  - There is no satisfactory method of diagnosis, prevention or treatment of the condition OR the medicine is of significant benefit to those affected by the condition.

- Consult EMA!

European Medicines Agency - EMA

- Timeline:

COMP: Committee for Orphan Medicinal Products
SAWP: Scientific Advice Working Party



Source: EMA website

Lessons learnt*

- Commercial impact should be expected
  - Provide a clear business plan, marketing strategy, market analysis and time-to market estimation.
  - Involve SME/industrial partner to take the product ahead beyond the project's end.
- Show clear advantage over existing treatment (both medically and commercially).
- Build a strong and complementary consortium, including partners with good track record and experience in clinical trials.
- Involve patient advocacy groups
- Provide a good and clear trial design, specifically statistical analysis and sample size calculation.
- The project should be focused and any deviation or additional activity (e.g. secondary trials) should be strongly justified and appropriate to the topic.

* Could be topic-specific

Lessons learnt*

- Patient safety: provide risk/benefit considerations, stopping criteria, explain how you will deal with adverse events, etc.
- Provide a realistic timeline for regulatory approvals.
- Show that you are able to produce results which will be advantageous even if outcomes of trial are negative (e.g. databases, new biomarkers of recovery)
- Show relation and continuity from FP7/other past projects when relevant.
- Shipping cells/tissue samples between centres/partners is a complicated issue – plan adequately, consider budget, logistics and regulatory issues.

* Could be topic-specific

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