EARMA
EUROPEAN ASSOCIATION OF
RESEARCH MANAGERS AND ADMINISTRATORS

Clinical Trials

Clinical Trials in Horizon 2020

Yoram Bar Zeev
ybz@beacontech.eu
Yasmin Wachs
yasmin.wachs@beacontech.eu

beacontech
Research & Innovation Management

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

beaontech
Research & Innovation Management

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:
  - Normally "Per patient" basis, allowing competitive recruitment
  - Profit might be included
- Many people are involved
- Clinical Trial monitoring is essential - CRO
- Data analysis
- Sponsorship and insurance

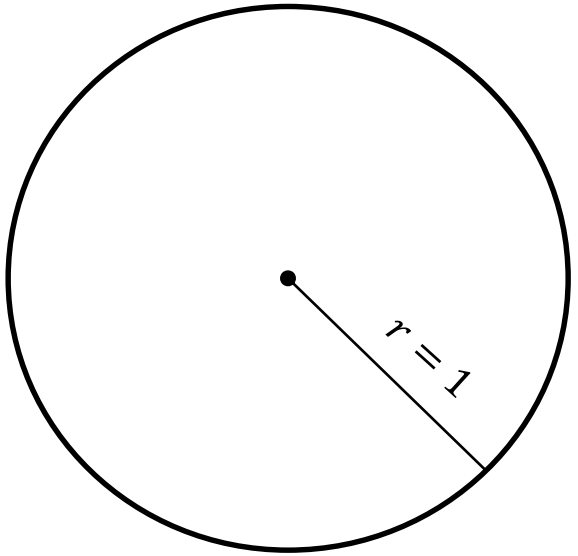
Clinical Research Organization

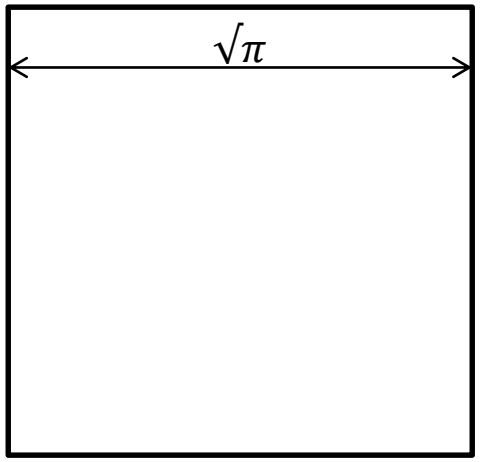
- Typical roles of CRO:
  - Patient recruitment management
  - Clinical Trial monitoring
  - Regulatory affairs / support (e.g. IRB, communication with competent authorities)
  - Data analysis and statistics
- Represent core expertise in managing Clinical Trials
- "For profit" companies and "Academic"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

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

Squaring the circle

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 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
  - Define sub-populations if subgroup analysis is planned
- *Statistic analysis planning and power calculation*
- *Cumulative safety information*
  - Pre-clinical data from in-vitro or in-vivo studies; data from previous clinical studies; data from (pharmaco-)vigilance systems
- *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
  - 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*

European Medicines Agency - EMA

- The European Medicines Agency (EMA) is the European Union agency for ***the evaluation of medicinal products***
- Under the call for "New therapies for rare diseases", applicants need to show a granted ***orphan designation*** and 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:

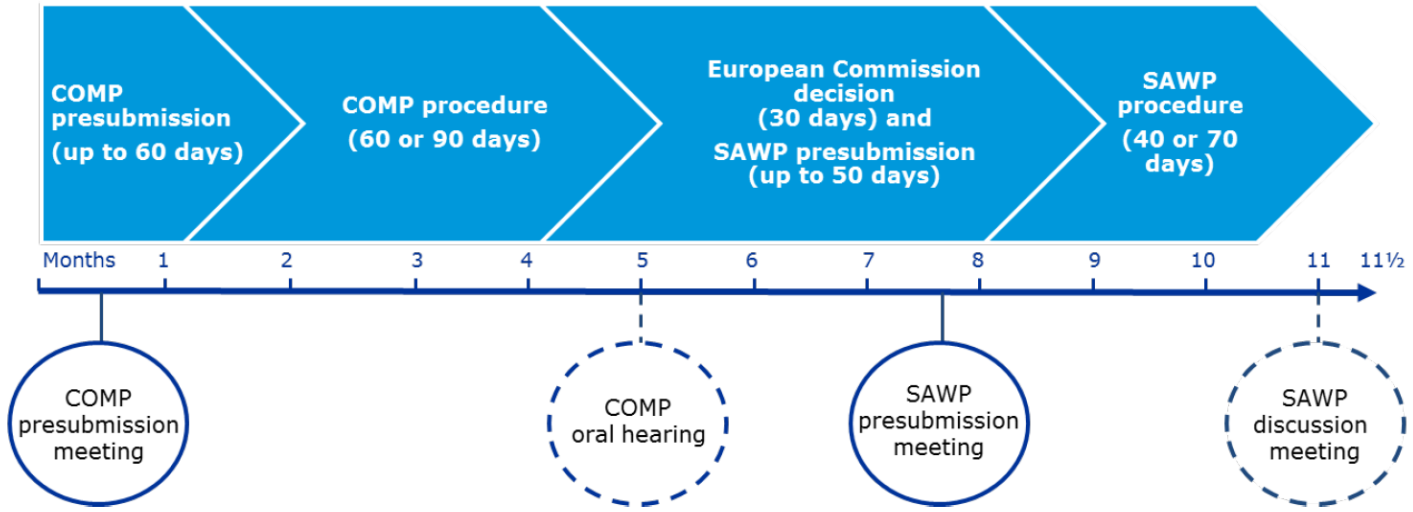
- Targeting a disease that is life-threatening or chronically debilitating
- Prevalence not more than 5 in 10,000 (rare disease)
- There is no satisfactory method of diagnosis, prevention or treatment of the condition OR the medicine is of significant benefit to those affected by the condition.

- Consult EMA

European Medicines Agency - EMA

Timeline:

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

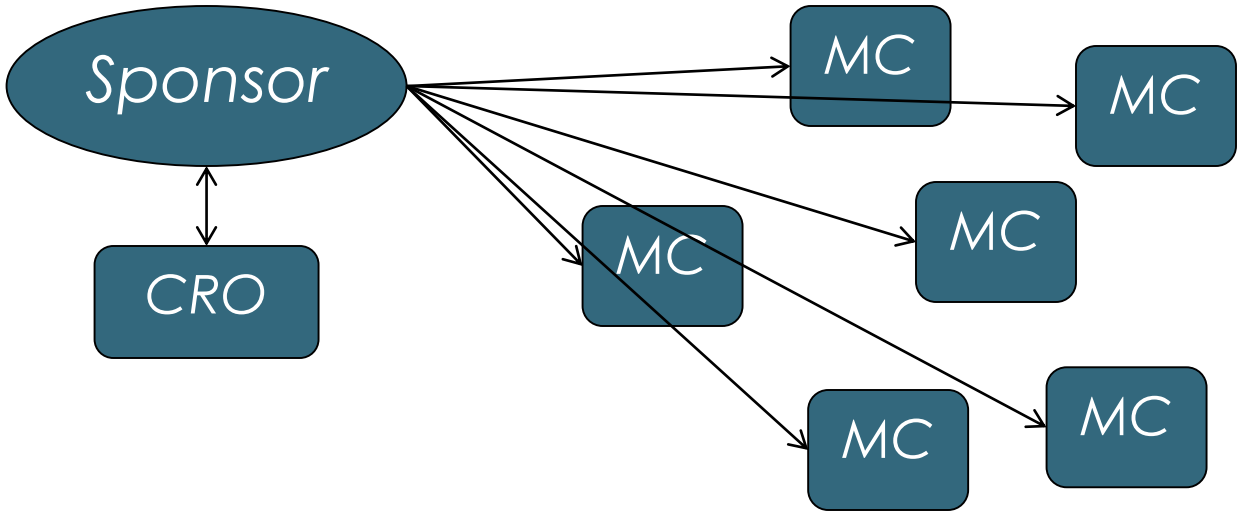


Source: EMA website

Squaring the circle

H2020 funding vs. Clinical Trial payment structure

A typical Clinical Trial:



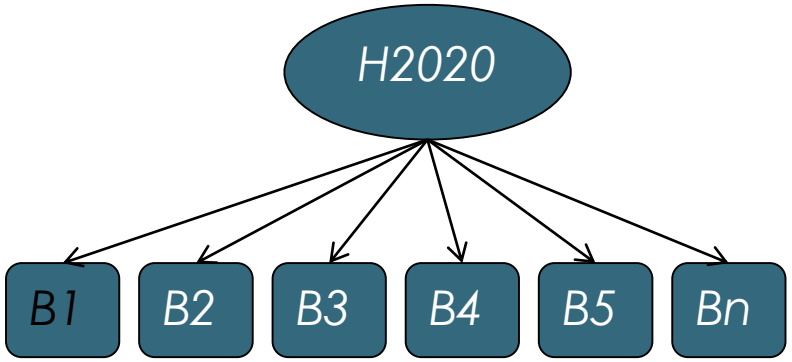
- Medical Centers can be pre-defined or recruited Ad-Hoc
- Competitive recruitment of patients
- Pay per patient = Ongoing payment

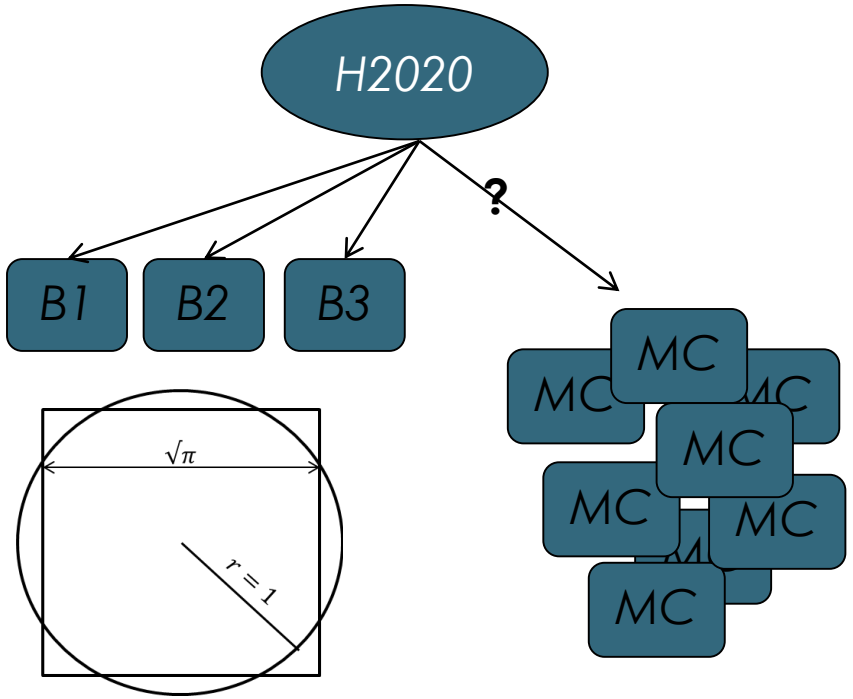
Squaring the circle

H2020 funding vs. Clinical Trial payment structure

In H2020:

- Each beneficiary is paid once in each reporting period
- 2-4 payments/periods throughout the project



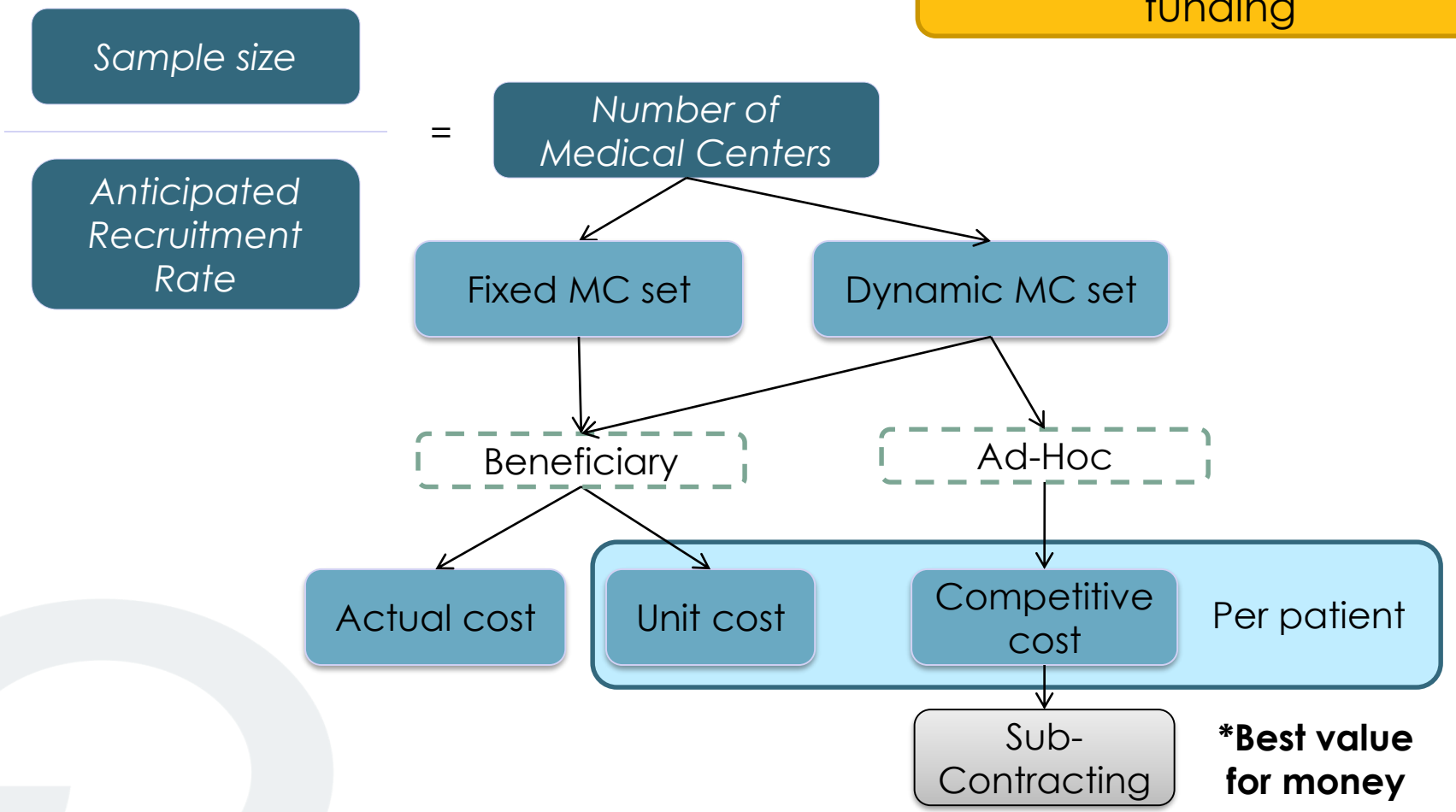


Squaring the circle

H2020 funding vs. Clinical Trial payment structure

The motivation: Pay Per Patient

Orchestrating the MC funding



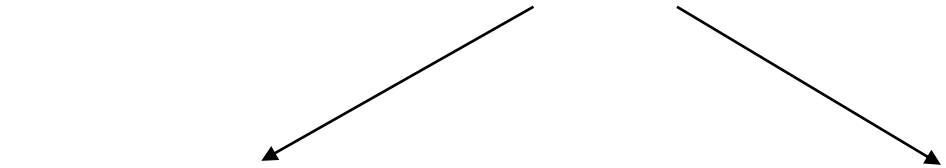
***Best value for money**

Squaring the circle

H2020 funding vs. Clinical Trial payment structure

H2020 Unit cost ≠ Typical clinical trial per-patient payment

H2020 Unit cost = {A} x {B}



Reference unit:
1 hour of MD,
1 blood test,
etc.

Cost of unit in accounting year N-1 (according to documented evidence)

- Once defined and approved – no need to justify
- The N-1 problem
- Lack of flexibility: {A} and {B} cannot be modified during the project

Sub-contracting in Clinical Trials

beacontech
Research & Innovation Management

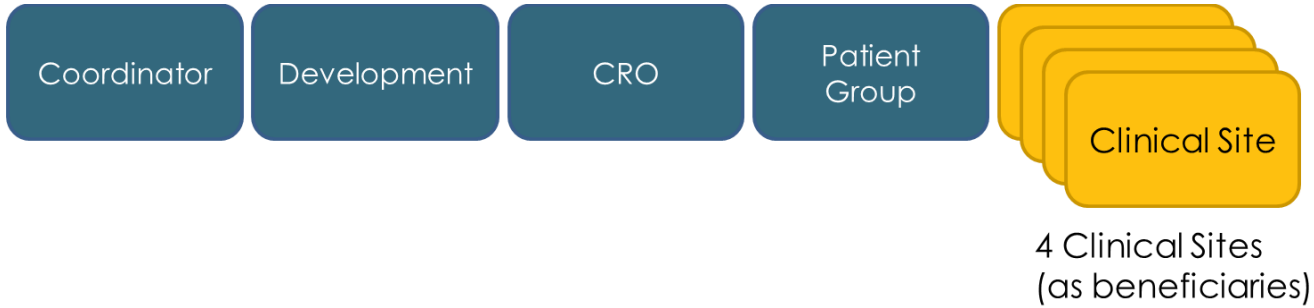
- Sub-contracting is known to be unwelcome in Horizon 2020
- The big exception is in Clinical Trials
- Sub-contracting in Clinical Trial is welcome for:
  - CRO
  - Clinical sites
- Best value for money must be proven
- It allows to include profit

- Plan with care

Squaring the circle

Fixed consortium structure vs.
Competitive recruitment of patients

Fixed Medical Centers and consortium set :



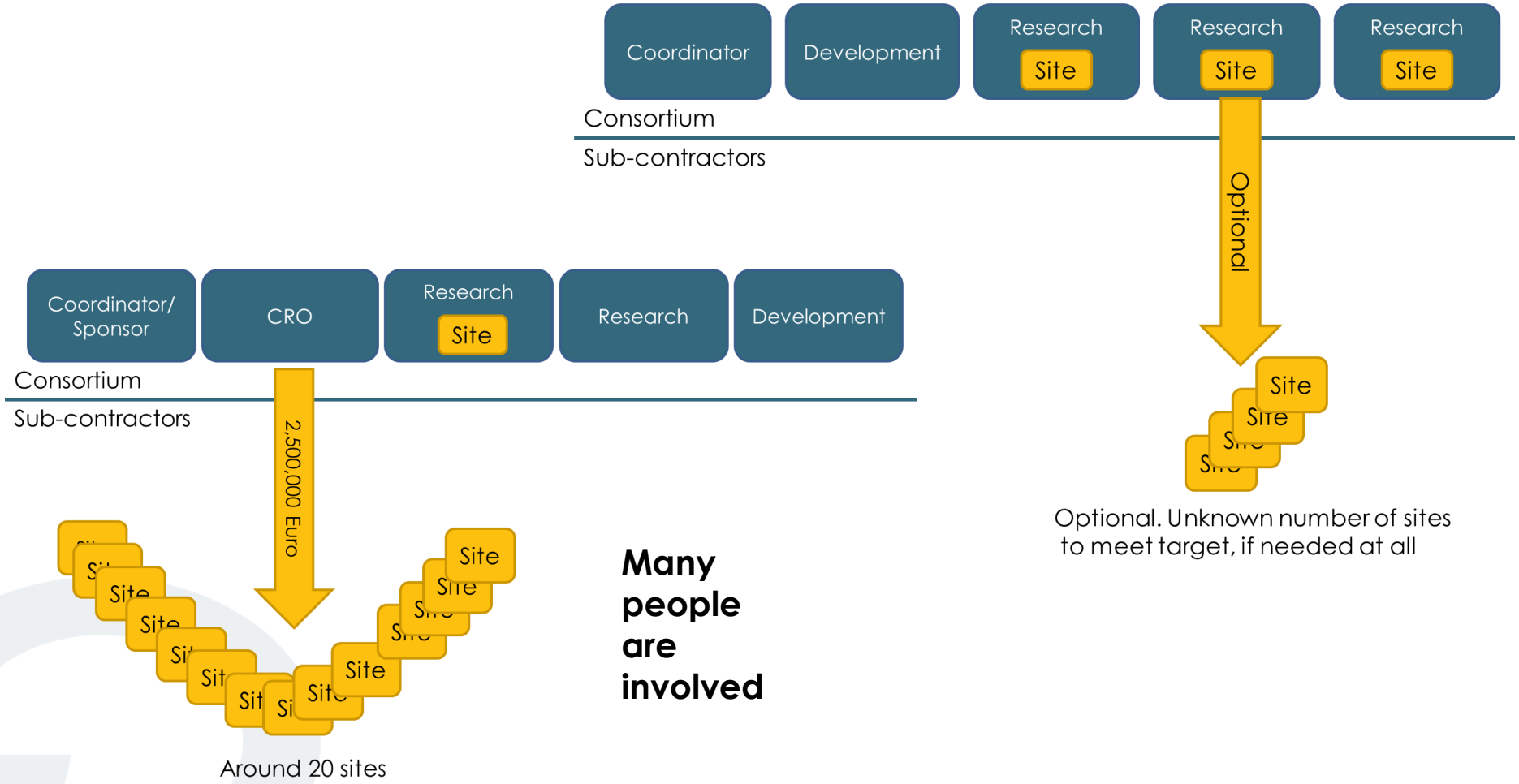
4 Clinical Sites
(as beneficiaries)

7 Clinical Sites
(as beneficiaries)

Squaring the circle

Fixed consortium structure vs.
Competitive recruitment of patients

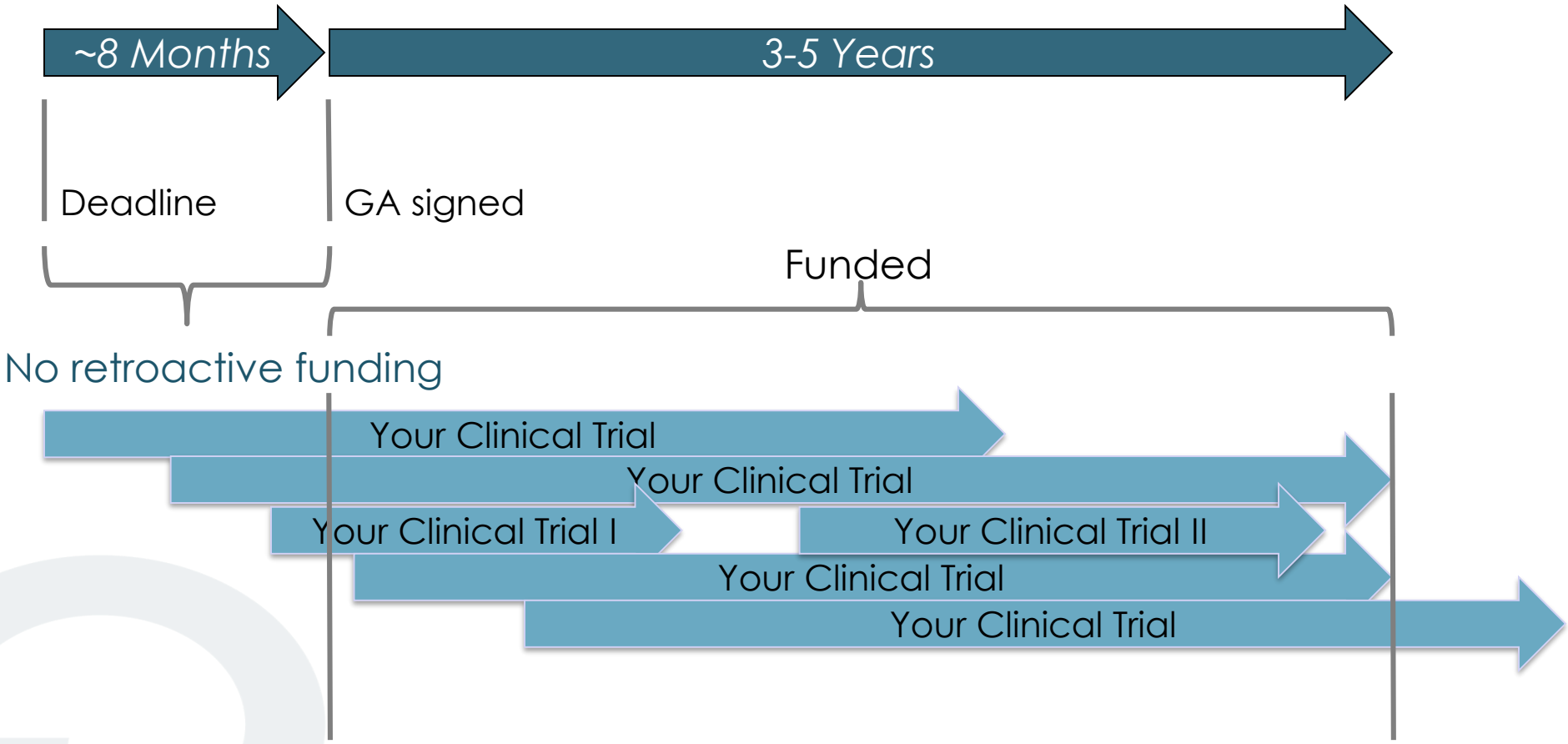
Dynamic Medical Centers set :



Many people are involved

Squaring the circle

Typical and strict RIA duration vs.
variable clinical trial timeframes



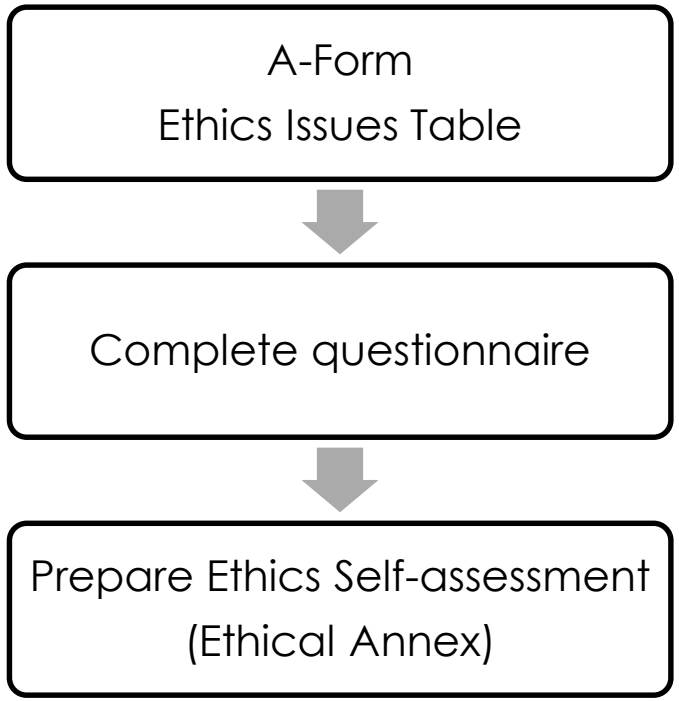
Legal and Ethical aspects

- 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"



beaontech
Research & Innovation Management

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

beaontech
Research & Innovation Management

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

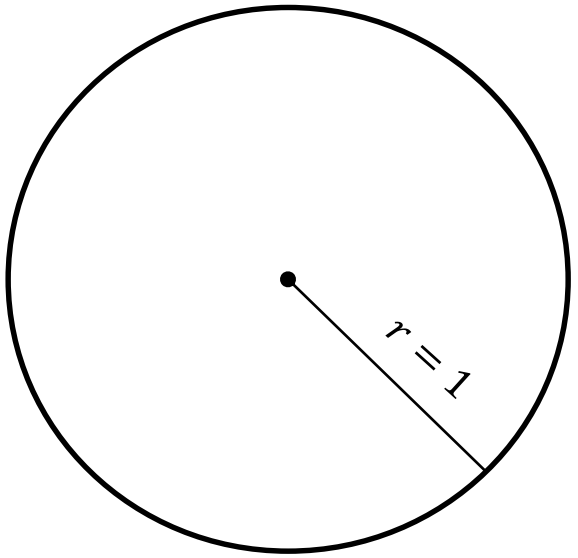
- For what use?

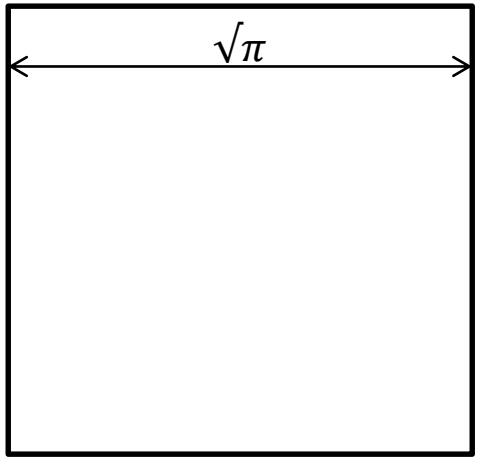
- Justification for choice of species
- 3Rs, precise evaluation of number
- Description of procedure, husbandry, anaesthesia, euthanasia
- applicable legislation

- Documents to provide

- ethics authorisations / project license
- personal and laboratory licenses

The main thing to remember:





2016 submitted proposals

beaontech
Research & Innovation Management

In topics directly related to clinical trials

Topic		Submitted proposals	Allocated budget
SC1-PM-01-2016	**Multi omics for personalised therapies addressing diseases of the immune system**	16	30 M€
SC1-PM-06-2016	**Vaccine development for malaria and/or neglected infectious diseases**	42	40 M€
SC1-PM-09-2016	**New therapies for chronic diseases**	138	60 M€
SC1-PM-11-2016-2017	**Clinical research on regenerative medicine**	32	30 M€ (2016)

Health, demographic change and well-being

Treating And Managing Diseases

Clinical Trial-focused topics for 2017

SC1-PM-08–2017: New therapies for rare diseases

- **EC Orphan designation** should be in place by the deadline (2nd stage), and recommendations from **protocol assistance** given by EMA should be implemented in the trial design.
- Clinical trials may focus on a range of interventions from small molecule to gene or cell therapy
- Can include novel interventions and/or repurposing of existing and known interventions
- May also include limited elements of late stage preclinical research and/or experimental evaluation of potential risks
- Should provide a clear patient recruitment strategy

Deadline: 04 Oct 2016 (First stage), 11 Apr 2017 (Second stage)

Budget per topic: 60 M€, per project: 4-6 M€

European Medicines Agency - EMA

beaontech Research & Innovation Management

COMP timeline:

Deadline for submission of applications	Start of procedure - day 1 (for validated applications)	COMP* meeting (see note below)
23 May 2016	13 June 2016	6-8 September 2016
24 June 2016	18 July 2016	4-6 October 2016
20 July 2016	15 August 2016	3-4 November 2016
30 August 2016	12 September 2016	6-8 December 2016

SAWP timeline:

Start of procedure SAWP meeting	**Presubmission meeting**			**Final briefing package by**	**SAWP 1** **start of procedure**	**SAWP 2** **reports discussed**	**Finalisation day 40** **adoption at CHMP**	**SAWP 3 if needed** **meeting with applicant**	**Finalisation day 70** **adoption at CHMP**	**Finalisation for PASS procedures only**
	YES		NO							
	Letter of Intent and draft briefing package by	*Dates of presubmission meeting*	Letter of Intent and draft briefing package by							
26 – 29 Sep 16	08 Aug 16	*15 Aug 16 – 16 Sep 16*	05 Sep 16	21 Sep 16	26 – 29 Sep 16	24 – 27 Oct 16	07 – 10 Nov 16	28 Nov – 01 Dec 16	12 – 15 Dec 16	09 – 12 Jan 17
24 – 27 Oct 16	05 Sep 16	*12 Sep 16 – 14 Oct 16*	03 Oct 16	19 Oct 16	24 – 27 Oct 16	28 Nov – 01 Dec 16	12 – 15 Dec 16	09 – 12 Jan 17	23 – 26 Jan 17	06 – 09 Feb 17
28 Nov – 01 Dec 16	03 Oct 16	*10 Oct 16 – 18 Nov 16*	07 Nov 16	23 Nov 16	28 Nov – 01 Dec 16	09 – 12 Jan 17	23 – 26 Jan 17	06 – 09 Feb 17	20 – 23 Feb 17	06 – 09 Mar 17

Source: EMA website

SC1-PM-10–2017: Comparing the effectiveness of existing healthcare interventions in the adult population

- Compare the use of currently available preventative or therapeutic (pharmacological as well as non-pharmacological) healthcare interventions in adults
- Preference will be given to interventions with high public health relevance and socio-economic impact
- Contribute to improve interventions, and provide recommendations on the most effective and cost-effective approaches
- Outcomes such as quality of life, patient mortality, morbidity, costs and performance of the health systems should be assessed

Deadline: 04 Oct 2016 (First stage), 11 Apr 2017 (Second stage)

Budget per topic: 40 M€, per project: 4-6 M€

SC1-PM-11–2016-2017: Clinical research on regenerative medicine

- Regenerative medicine therapies which are ready for clinical (in-patient) research
- Any stage of clinical work (e.g., first in man, late stage trial, observational study) may be proposed though *later stages are preferred*
- Appropriate preliminary data should be presented according to the clinical phase proposed (e.g. preclinical evidence for phase I proposals).
- Ethical approvals (IRB) should be in place for clinical work to start.
- Proposals should justify why the therapy proposed is regenerative and how it represents a new approach compared to any existing treatment

Deadline: to be published (full proposal)

Budget per topic (2017): 30 M€, per project: 4-6 M€

Health, demographic change and well-being

Additional relevant topics (2017)

SC1-PM-02-2017: New concepts in patient stratification

- Deliver novel concepts for disease-mechanism based patient stratification to address the needs for stratified or personalised therapeutic interventions.
- Integrate multidimensional and longitudinal data and harness the power of -omics, including pharmacogenomics, systems biomedicine approaches, network analysis and of computational modelling.
- The new concepts of stratification should be validated in pre-clinical and clinical studies taking into account sex and gender differences
- Focus on complex diseases having high prevalence and high economic impact

Deadline: 04 Oct 2016 (First stage), 11 Apr 2017 (Second stage)

Budget per topic: 40 M€, per project: 4-6 M€

SC1-PM-07-2017: Promoting mental health and well-being in the young

- Population-oriented primary prevention interventions to promote mental well-being of young people (up to 25) and assess them for their effectiveness
- Build on existing state-of-the art knowledge (and go beyond it) on biological, psychological and social determinants of mental well-being (societal, cultural, work life, lifestyle, epidemiological, economic and environmental perspectives).
- Research design should involve the young themselves, gathering their input through innovative approaches.
- Interventions should should reflect the diversity of the different countries and regions in Europe and should take gender and health inequality aspects into account

Deadline: 04 Oct 2016 (First stage), 11 Apr 2017 (Second stage)

Budget per topic: 20 M€, per project: 4-6 M€

Food security, sustainable agriculture and forestry, marine and maritime and inland water research and the bioeconomy

Healthy and safe foods and diets for all

Additional relevant topics

SFS-39-2017: How to tackle the childhood obesity epidemic?

- Aim at innovative and efficient strategies, tools and/or programmes for promoting sustainable and healthy dietary behaviours and lifestyles.
- Focus on specific target groups in the young (e.g., during pregnancy and foetal development, in infants, toddlers, adolescents).
- Combine different disciplines (e.g. (epi)genetics, molecular biology, microbiome, gut-brain signalling, physiology, nutrition, physical activity sciences, information and communication technology, social sciences and humanities, education, environment, architectural and urban design, psychology).
- Partners from US, Australia, New Zealand and Canada are encouraged

Deadline: 14 Feb 2017 (First stage) 13 Sep 2017 (Second stage)

Budget per topic: 20 M€, per project: up to 10 M€

SFS-40-2017: Sweeteners and sweetness enhancers

- Focus on health, obesity and safety aspects (including combined/prolonged use, metabolic effects and gut brain signalling, neuro-behaviour, and effects on the microbiota) associated with S&Ses
- Investigate consumer perceptions and preferences giving proper considering the underlying physiological, psychological and socio-economic drivers
- Include stakeholders from the food industry, including SMEs

Deadline: 14 Feb 2017 (First stage) 13 Sep 2017 (Second stage)

Budget per topic 9M€ , per project: up to 9M€

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

* In Clinical Trial focused projects

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

tech Management

beacontech
Research & Innovation Management

Yoram Bar Zeev ybz@beacontech.eu
Yasmin Wachs yasmin.wachs@beacontech.eu

Find us on LinkedIn