Organizing an academic clinical trial

Case study: ‘B-VOICE’

Vaccination against covid-19 in cancer patients under active treatment (Belgium)

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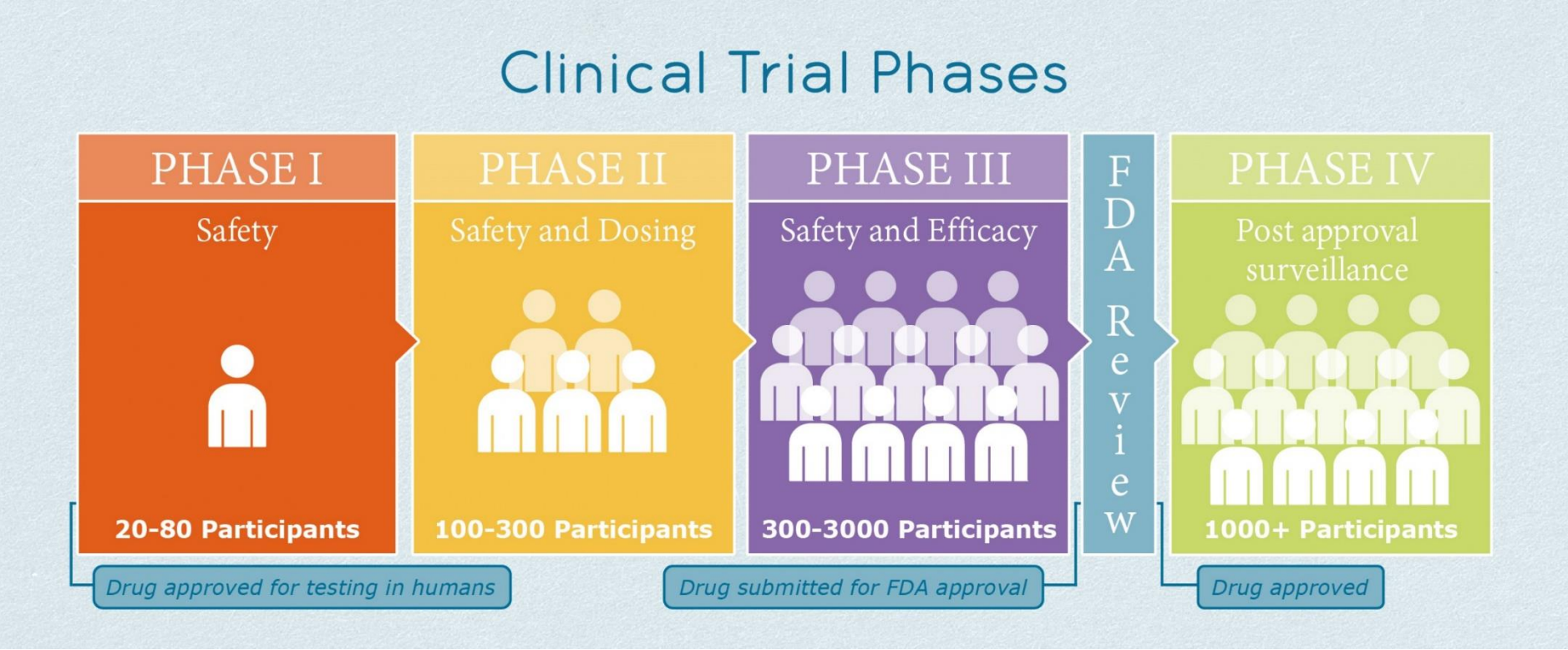
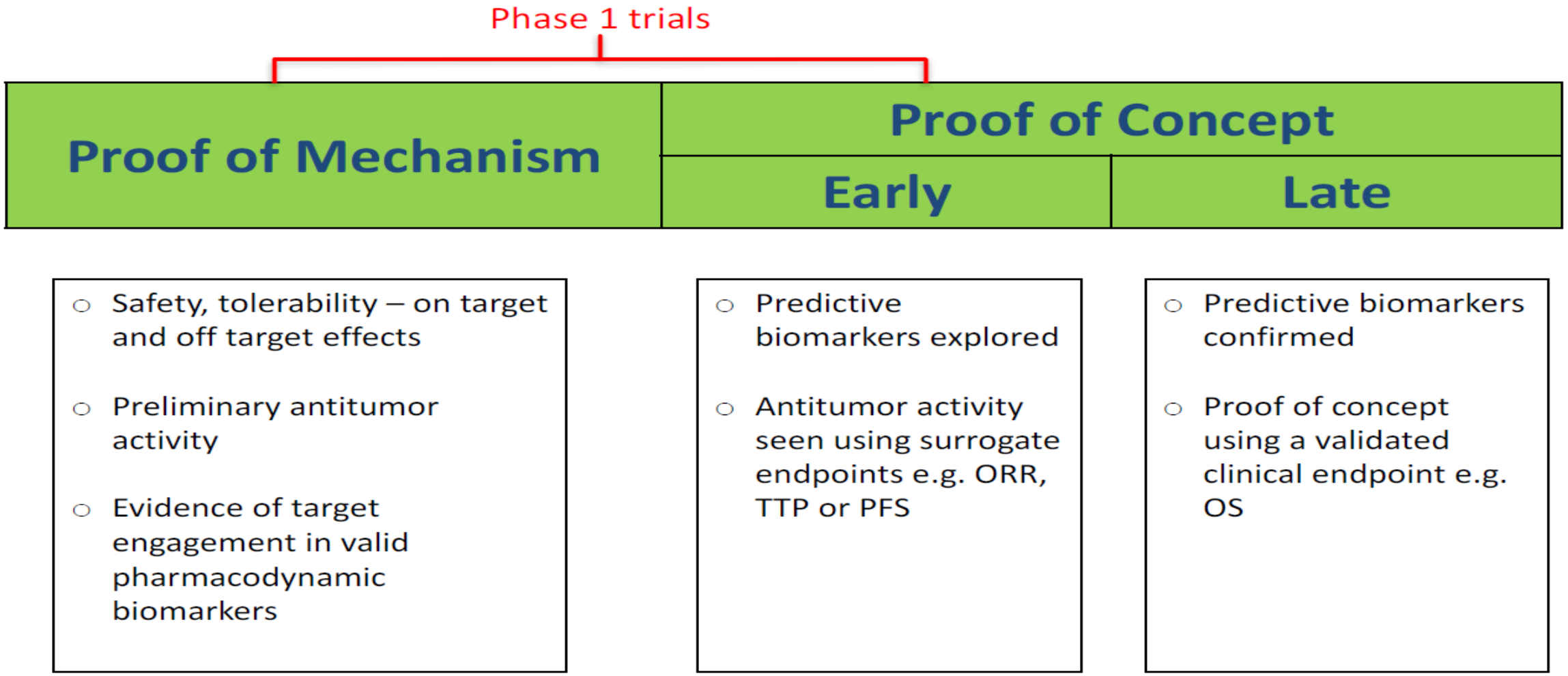
1. INTRODUCTION

Definition of a Clinical Trial

- A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.



New Paradigm of Drug Development



Courtesy of David Hong

2. STUDY RATIONALE

B-VOICE

- Cancer patients are at higher risk of developing COVID-19 respiratory disease + higher likelihood of poor disease outcomes
- State of immune system of cancer patients under active treatment might differ from individuals without cancer
- Understanding immunogenicity and durability of immune response after vaccination => provide guidelines for a vaccination strategy

CENTRAL QUESTION

- Can patients with cancer and especially those under active treatment develop protective immunity against COVID-19 upon vaccination?

3. PREPARATION TRIAL SETUP

I. Qualifications of Study Team

II. Study documents

III. Regulatory

IV. Trial Master File (TMF) and Investigator Site File (ISF)

3. PREPARATION TRIAL SETUP

I. Qualifications of Study Team

ICH-GCP

- ICH = International Council for Harmonisation of technical requirements for pharmaceuticals for human use
- GCP = Good Clinical Practice

WHY REGULATE CLINICAL RESEARCH?

To ensure

- Proper protection of study subjects
- Studies to be based on good scientific principles including a well-designed study protocol and proper statistical analysis of data
- Study procedures to be properly undertaken and documented

ICH-GCP GUIDELINE

- A standard for all aspects of clinical trials (design, conduct, performance, monitoring, auditing, recording, analyses, reporting) to ensure that:
  - Data and reported results are credible and accurate
  - Rights, integrity and confidentiality of clinical trial subjects are protected

3. PREPARATION TRIAL SETUP

II. Study documents

- Study protocol
- Investigator Brochure (IB)
- Informed Consent Form (ICF)
- (Electronic) Case Report Forms (eCRF)
- Documents provided to study patients (e.g. questionnaires, flyer, …)

3. PREPARATION TRIAL SETUP

III. Regulatory

- First step: apply for an EDGE number
- Second step: parallel submission
  - **Ethics Committee (EC)**
    - Submission for approval:
      - Initial submission: application form ethical committee, accompanying letter, protocol of the clinical trial, IB, informed consent for the patient, study patient documents, CV and GCP of principal investigator → when approved: EC number assigned to project
      - Subsequent submissions: protocol amendment, addition of sites, …
    - Annual progress report
  - **Regulatory authority (FAGG/AFMPS)**
    - EUDRACT number
    - In case of Investigational Medicinal Product
- Contracts:
  - Clinical Trial Agreement (CTA)
  - Other contracts

3. PREPARATION TRIAL SETUP

IV. Trial Master File (TMF) and Investigator Site File (ISF)

- Delegation Log, Training Log
- CV & GCP certificates study team
- Subject / patient documents: screening- and enrolment log, subject identification log, deviation log, …
- Laboratory and technical procedures
- Investigational Medicinal Product (IMP) related documents
- Monitoring plan
- Trial related procedures: e.g. statistical analysis plan (SAP), data management plan (DMP)
- …

4. INVESTIGATIONAL PLAN

I. Study design

II. Sampling and data collection

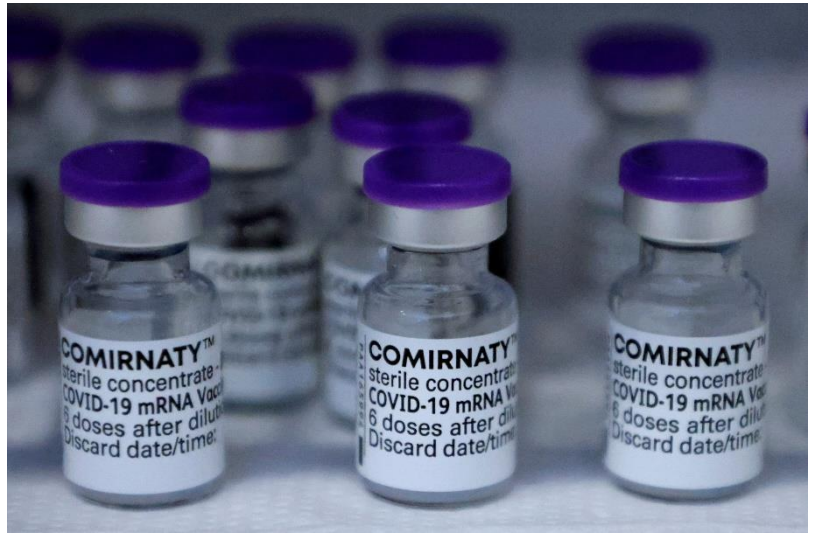
III. Safety reporting

4. INVESTIGATIONAL PLAN

I. Study design

- Prospective, multicohort interventional study
- B-VOICE: participants receive COVID-19 mRNA Vaccine BNT162b2 (Comirnaty®)
- B-VOICE PLUS: participants receive COVID-19 Viral Vector-based AstraZeneca vaccine

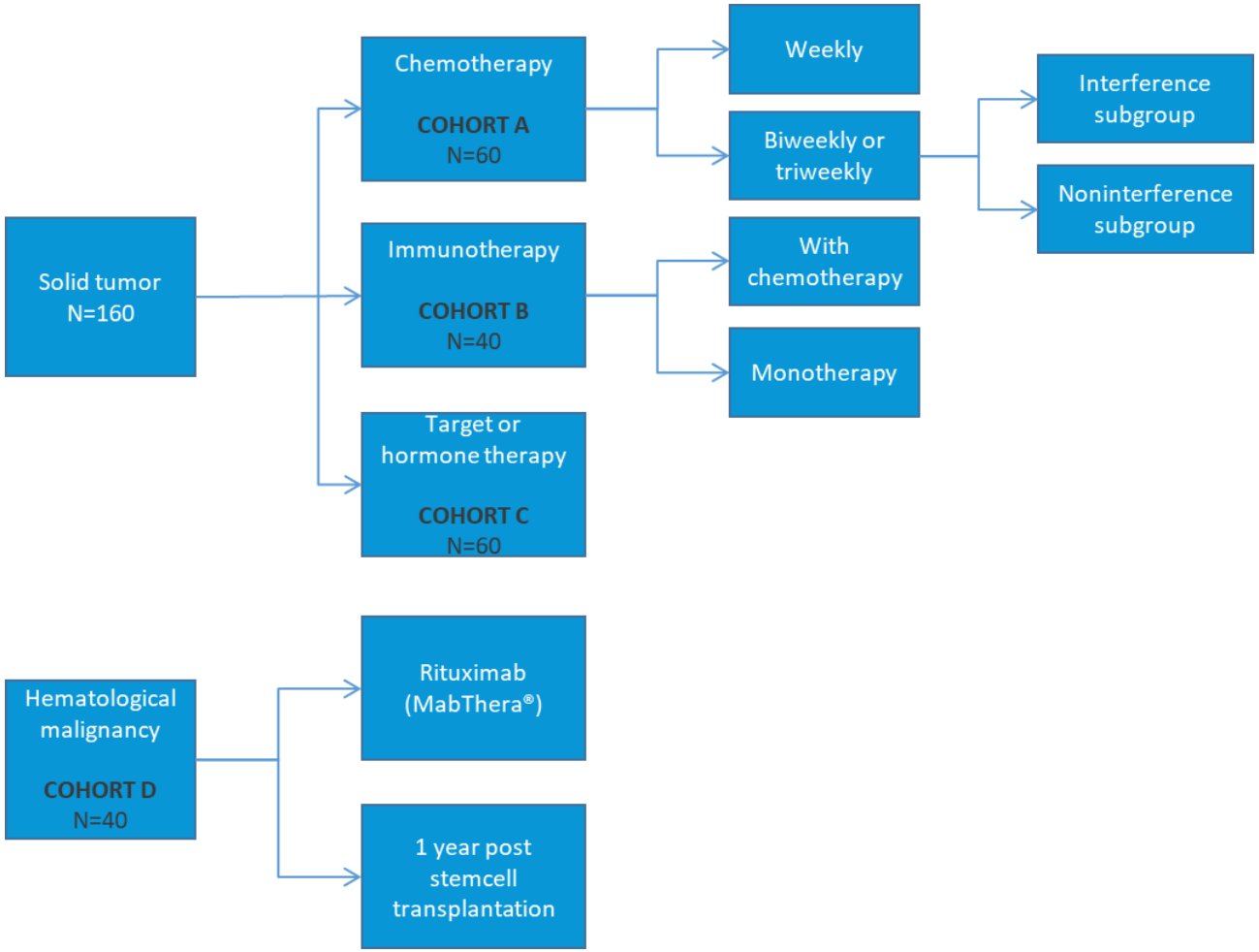
➔ Compare efficacy of two types of vaccines



4. INVESTIGATIONAL PLAN

I. Study design

- Overview of the cohorts included in this study and their subdivisions



4. INVESTIGATIONAL PLAN

I. Study design

- Cohort A: solid tumor under active chemotherapy as monotherapy
  - Important to know if vaccination timing matters
  - Interference subgroup: vaccine day 8 post-chemotherapy administration => weekly chemotherapy regimen always in interference subgroup
  - Non interference subgroup: vaccine on day 2 before a new cycle

- Cohort B: solid tumor under active immunotherapy with or without chemotherapy
  - No existing evidence nor recommendation about timing of vaccine administration
  - Explore potential differences in immune response between immunotherapy as monotherapy and immunotherapy in combination with chemotherapy

- Cohort C: solid tumor receiving targeted therapy or hormone therapy without further specifications

- Cohort D: hematological malignancy receiving Rituximab (MabThera®) and patients +/- one year after hematopoietic stem cell transplantation

4. INVESTIGATIONAL PLAN

II. Sampling and data collection

- Timelines and content of samples (see table)
- Patient data are collected in a continuously routine manner through the RemeCare Oncology application
- B-VOICE:

B-VOICE	Screening (**)	$D_1$0	$D_1$1	$D_2$0 (***)	$D_2$7 (±2d)	$D_2$28 (±2d)	month 6 (±10d)	up to month 12	OBJECTIVES
SAMPLING SCHEME									
5ml dry serum tube		x	x	x	x	x	x		Humoral immune response: antibodies [a]
3*9ml heparin tubes		x	x	x	x	x	x		Cellular immune response (T and B cell) [b]
2.5ml PAX gene tube		x	x						Collection and storage
5ml EDTA whole blood tube		x							Routine hematology [c] and immune cell phenotyping [d]
Nasopharyngeal swap		In case of COVID-19 symptoms (*)							COVID diagnostics
DATA COLLECTION SCHEME									
Informed consent	x								
Inclusion/exclusion	x								
Medical history	x								
Comorbidities [e]	x				x		x	x	
Vaccine administration (after sampling)		dose 1		dose 2					
RemeCare Oncology	App BASED COLLECTION								
* Redness at the injection site		3-5d after each injection							
* Concomitant medication	Continuous								
* Smoking history		x							
* ECOG		x							
* BMI		x							
* Vital signs [f]	Continuous								
* (S)AEs	Continuous								
* COVID-19 questionnaire [g]	x				x	x	x	x	

(a) Serological assays for virus specific neutralizing antibodies and non-neutralizing antibodies
(b) Pheripheral blood mononucler cell (PBMC) isolation for cellular immunity
(c) Hemoglobin, red blood cell count, platelet count, white blood cell count, white blood cell differential
(d) Flowcytometry
(e) Hypertensia, diabetes, coronary artery disease, auto-immune disease, nephrological disease
(f) Vital signs: blood pressure, heart rate, temperature
(g) Nine COVID-19 related questions

(*) PCR confirmed infection
(**) Screening should be performed within 28 days prior to the first vaccination but can be done on the same day as the first vaccination.
(***) $D_2$0 is 21 days (+/-2d) from $D_1$0 except for Cohort A under biweekly or triweekly chemotherapy where $D_2$0 depends on the individual cycle regimen (see paragraph 3.1)
D_1: Timing with respect to the administration of the first dose of the vaccin
D_2: Timing with respect to the administration of the second dose of the vaccin

4. INVESTIGATIONAL PLAN

II. Sampling and data collection

- B-VOICE PLUS: extra citrate tube (rare cases of blood clots)

B-VOICE plus	Screening(*)	$D_1$0	$D_1$1	$D_1$21 (±2d)	$D_2$0 (**) (±2d)	$D_2$28 (±2d)	month 6 (±10d)	up to month 12
SAMPLING SCHEME								
5ml dry serum tube (a)		x	x	x	x	x	x	
3*9ml heparin tubes (b)		x	x	x	x	x	x	
1*3ml citrate tube (c)		x	x	x	x	x		
2.5ml PAX gene tube		x	x					
5ml EDTA whole blood tube (d)		x						
Nasopharyngeal swap		In case of COVID-19 symptoms (***)						
DATA COLLECTION SCHEME								
Informed consent	x							
Inclusion/exclusion	x							
Medical history	x							
Comorbidities (e)	x				x		x	x
Vaccine administration (after sampling)		dose1			dose2			
RemeCare Oncology	App BASED COLLECTION							
* Redness at the injection site		3-5d after each injection						
* Concomitant medication	Continuous							
* Smoking history		x						
* ECOG		x						
* BMI		x						
* Vital signs (f)	Continuous							
* (S)AEs	Continuous							
* COVID-19 questionnaire (g)	x				x	x	x	x

(a) Serological assays for virus specific neutralizing antibodies and non-neutralizing antibodies
(b) Pheripheral blood mononucler cell (PBMC) isolation for cellular immunity (T-cell and B-cell)
(c) Coagulation factors: APTT (activated partial thromboplastin time), PT (prothrombine Time), D-dimers and fibrinogen
(d) Flow cytometry and routine hematology (Hemoglobin, red blood cell count, platelet count, white blood cell count, white blood cell differential)
(e) Hypertensia, diabetes, coronary artery disease, auto-immune disease, nephrological disease
(f) Vital signs: blood pressure, heart rate, temperature
(g) Nine COVID-19 related questions
(*) Screening should be performed within 28 days prior to the first vaccination but can
(**) $D_2$0 is 12weeks (+/-2d) from $D_1$0
(***) PCR confirmed infection
D_1: Timing with respect to the administration of the first dose of the vaccine
D_2: Timing with respect to the administration of the second dose of the vaccine

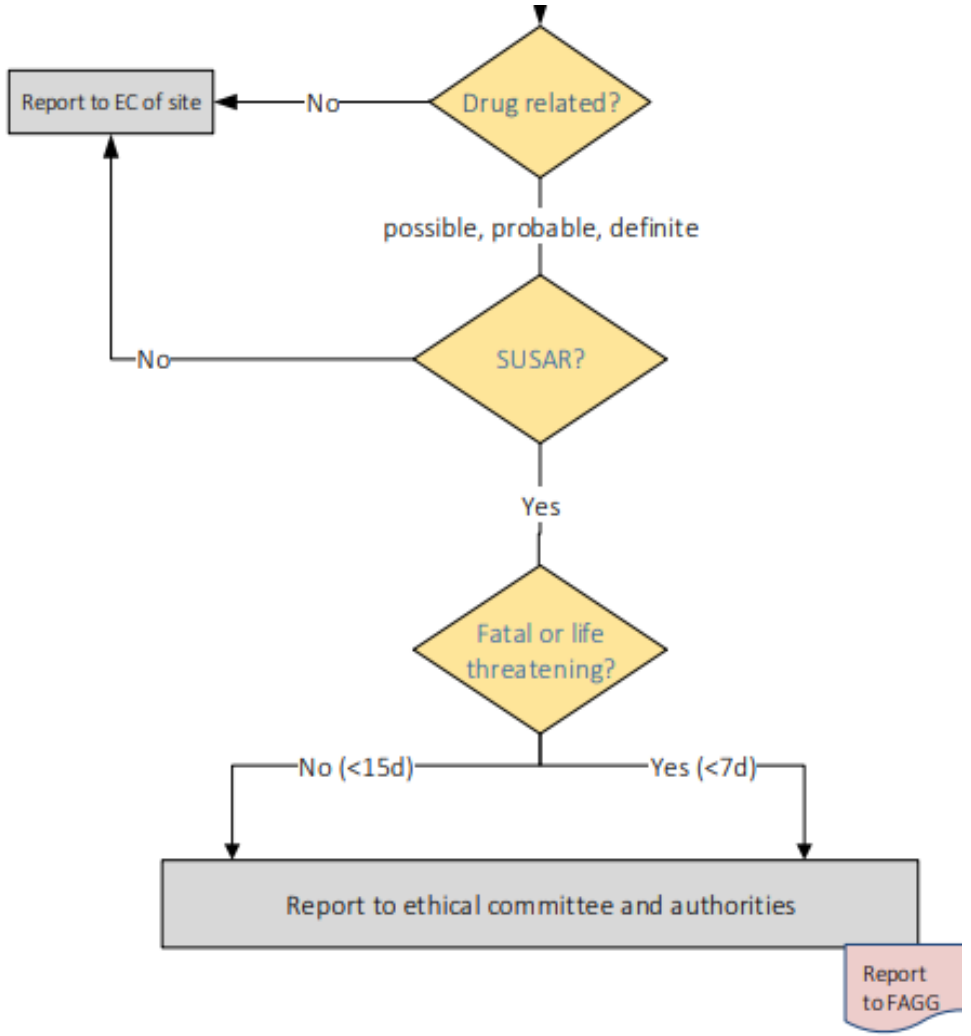
4. INVESTIGATIONAL PLAN

III. Safety reporting

- Adverse events (**AEs**): any undesirable experience occurring to a subject during the study, whether or not considered related to COVID-19 vaccination
- A serious adverse event (**SAE**): any unwanted medical effect that:
  - results in death;
  - is life threatening (at the time of the event);
  - requires hospitalization or prolongation of existing inpatients' hospitalization;
  - results in persistent or significant disability or incapacity;
  - any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.
- Adverse events of special interest (**AESIs**): events thought to be [potentially] associated with the investigational compound or disease under study

4. INVESTIGATIONAL PLAN

III. Safety reporting



5. STUDY POPULATION: inclusion and exclusion criteria

Inclusion criteria

- Age of 18 years or older
- Patients should meet one of the cohort criteria
- Life expectancy > 6 months
- Ability to provide informed consent

Exclusion criteria

- Women who are pregnant or breastfeeding
- Immune deficiency not related to cancer or cancer treatment
- Allergy (multiple)

6. STUDY ENDPOINTS

PRIMARY ENDPOINTS

- Quantification of different anti-SARS-CoV-2 specific IgG antibodies after vaccination (day 28 after the second dose) in patients receiving active cancer treatment
  - Antibody titers to full Spike, S1, S2, RBD (receptor binding domain) and N (nucleocapsid) protein of SARS-COV-2

- Response => patients will be classified as responders or non-responders

- Methodology
  - Multiplex SARS-COV-2 Immunoassay
  - Anti-RBD IgG (best correlation with in vitro neutralisation) => in house anti-RBD IgG ELISA

6. STUDY ENDPOINTS

SECONDARY ENDPOINTS

- Study the **evolution and duration of immune response** after vaccination: using serology assays to analyze anti-RBD IgG titers performed at the moment of second dose administration and at 6 months after the first dose.
- Analyze the **titer of neutralizing antibodies** 28 days after the second dose as well as at 6 months after the first dose.
- Identify the most **optimal timing of vaccination** in patients under chemotherapy.
- Investigate the **efficacy of the immune response**: assessed by SARS-Cov2 infection rate based on information collected through questionnaires on incidence of (PCR-confirmed) SARS-CoV-2 infection within a time-frame of 12 months after start of study.
- In depth assessment of the immune response: measuring the SARS-Cov2 specific **T and B cell response** and its evolution and longevity
- Investigate the **safety** of COVID-19 vaccines: incidence and severity of systemic adverse events (AEs) during a continuous App based reporting system.

7. ORGANIZATIONAL PLAN

I. Study steps

- Patient screening: inclusion/exclusion criteria
- Obtaining Informed Consent
- Collection of medical history and comorbidities
- Scheduling dates vaccination & sampling
- Vaccine administration (first vaccination early February 2021)
- Blood sampling ~ sampling scheme
- Laboratory analysis and clinical data management
- Results on immune response using serology tests
- Answer to the central question

7. ORGANIZATIONAL PLAN

II. Structural organization

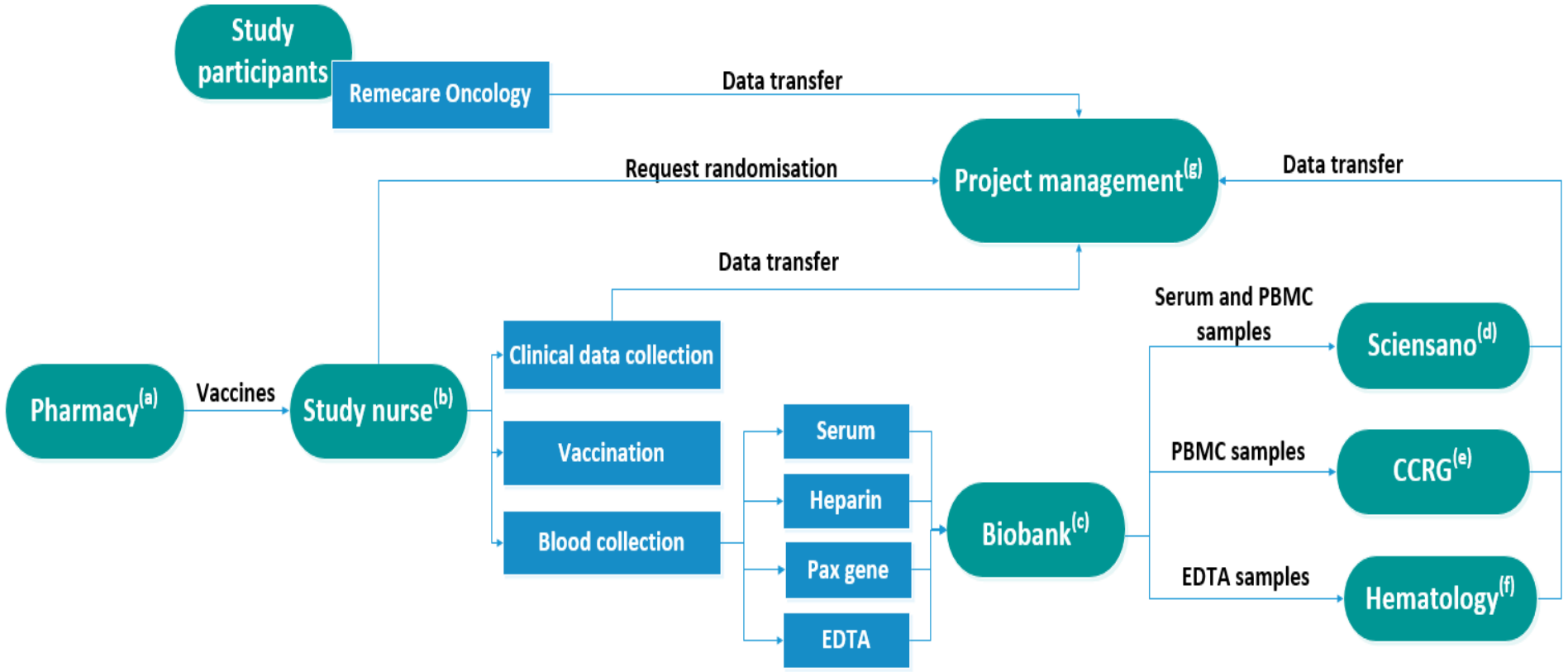
Principal responsibilities and activities:

- Data monitoring committee (DMC): independent of the entity conducting the project
  - Review results on safety among the different cohorts
  - Composed of experts of all relevant domains
  - Can recommend that early termination is needed
- Steering committee
- Operational:
  - Coordination
  - Patient logistics
  - Clinical project management
  - Biobanking
  - Pharmacy
- Statistics
- Partners (Remedus, Sciensano, …)

7. ORGANIZATIONAL PLAN

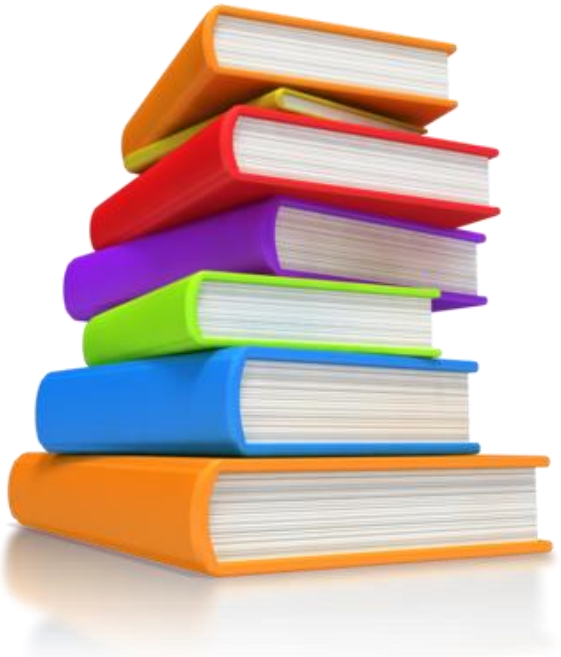
III. Logistical organization

Organization, planning, management and execution: Multidisciplinary Oncology Center Antwerp (MOCA) within UZA



8. STATISTICAL ANALYSIS

- Data sets are summarized in a descriptive way ➔ describing the immune response in a population of cancer patients
- Data and analysis are designed to be in line with PICOV-VAC study ➔ comparative analysis with a group of vaccinated healthy healthcare as control group
- Publication



Questions?