Biobanking at UZ / KU Leuven

27JAN2020

Loes Linsen

UZ Leuven | Herestraat 49 B - 3000 Leuven | www.uzleuven.be tel. +32 16 33 22 11 | UNIVERSITY HOSPITALS LEUVEN

Disclaimer

The information shown in this presentation reflects the legal framework and associated approach of the UZ KU Leuven Biobank on 27JAN2020.

Please consult our website for the current situation and actual documents in use.

https://www.uzleuven.be/nl/biobank-0 (regularly updated)

Scope

Biobank

Human bodily material for

Scientific research

NOT for therapeutic use (cell & tissue banks, ATMP)

Why is biobanking suddenly important?

- Sample quality
- Legal aspects & consequences

Translational Research Gap

- No confirmation of research results

How bad can it be?

Inability to reproduce scientific experiments is a big challenge.

Begley, C.G., Ellis, L.M. (2012). Drug development: Raise standards for preclinical cancer research. *Nature, 483(7391)*,531-533.

COMMENT

AVIAN INFLUENZA Shift expertise to track mutations where they emerge p.534 | EARTH SYSTEMS Past climates give valuable clues to future warming p.537 | HISTORY OF SCIENCE Descartes' lost letter tracked using Google p.540 | OBITUARY Wylie Vale and an elusive stress hormone p.542

Many landmark findings in preclinical oncology research are not reproducible, in part because of inadequate cell lines and animal models.

Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

AMGEN

BAYER

- Amgen could reproduce the findings in only 6 of 53 "landmark" papers in cancer biology
- Bayer could validate only 25% of 67 preclinical studies

REPRODUCIBILITY OF RESEARCH FINDINGS

Preclinical research generates many secondary publications, even when results cannot be reproduced.

Journal impact factor	Number of articles	Mean number of citations of non-reproduced articles*	Mean number of citations of reproduced articles
>20	21	248 (range 3–800)	231 (range 82–519)
5–19	32	169 (range 6–1,909)	13 (range 3–24)

Root causes for irreproducibility

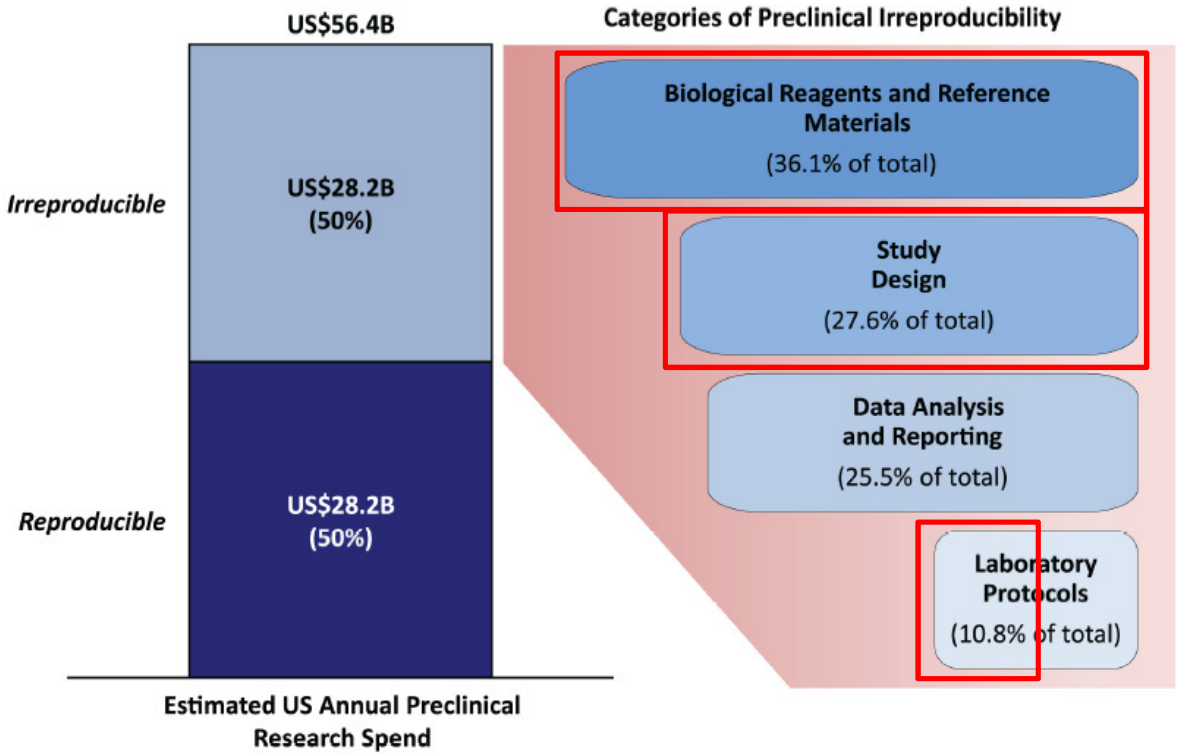


Fig 2. Estimated US preclinical research spend and categories of errors that contribute to irreproducibility. Note that the percentage value of error for each category is the midpoint of the high and low prevalence estimates for that category divided (weighted) by the sum of all midpoint error rates (see S1 Dataset). Source: Chakma et al. [18] and the American Association for the Advancement of Science (AAAS) [19].

(Freedman, L. et al. (2015) Plos Biology 13, e1002165.)

Why care about (sample) quality?

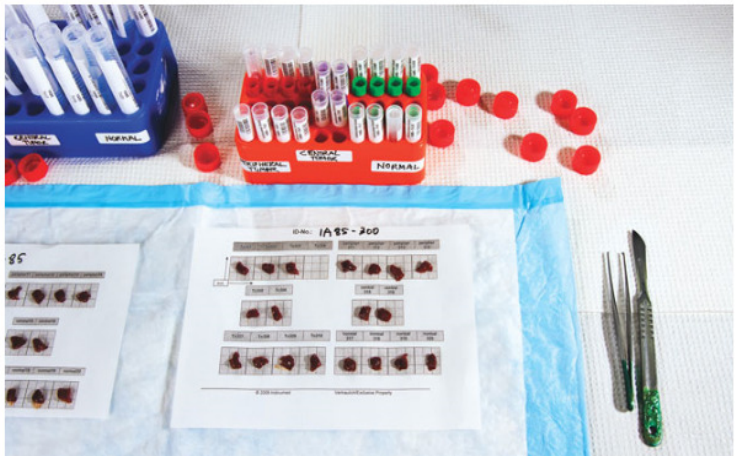
WIRED GEAR SCIENCE ENTERTAINMENT BUSINESS SECURITY DESIGN OPINION MAGAZINE

MAGAZINE | 18.06 | biobanks | cancer | Cancer Genome Atlas

Libraries of Flesh: The Sorry State of Human Tissue Storage

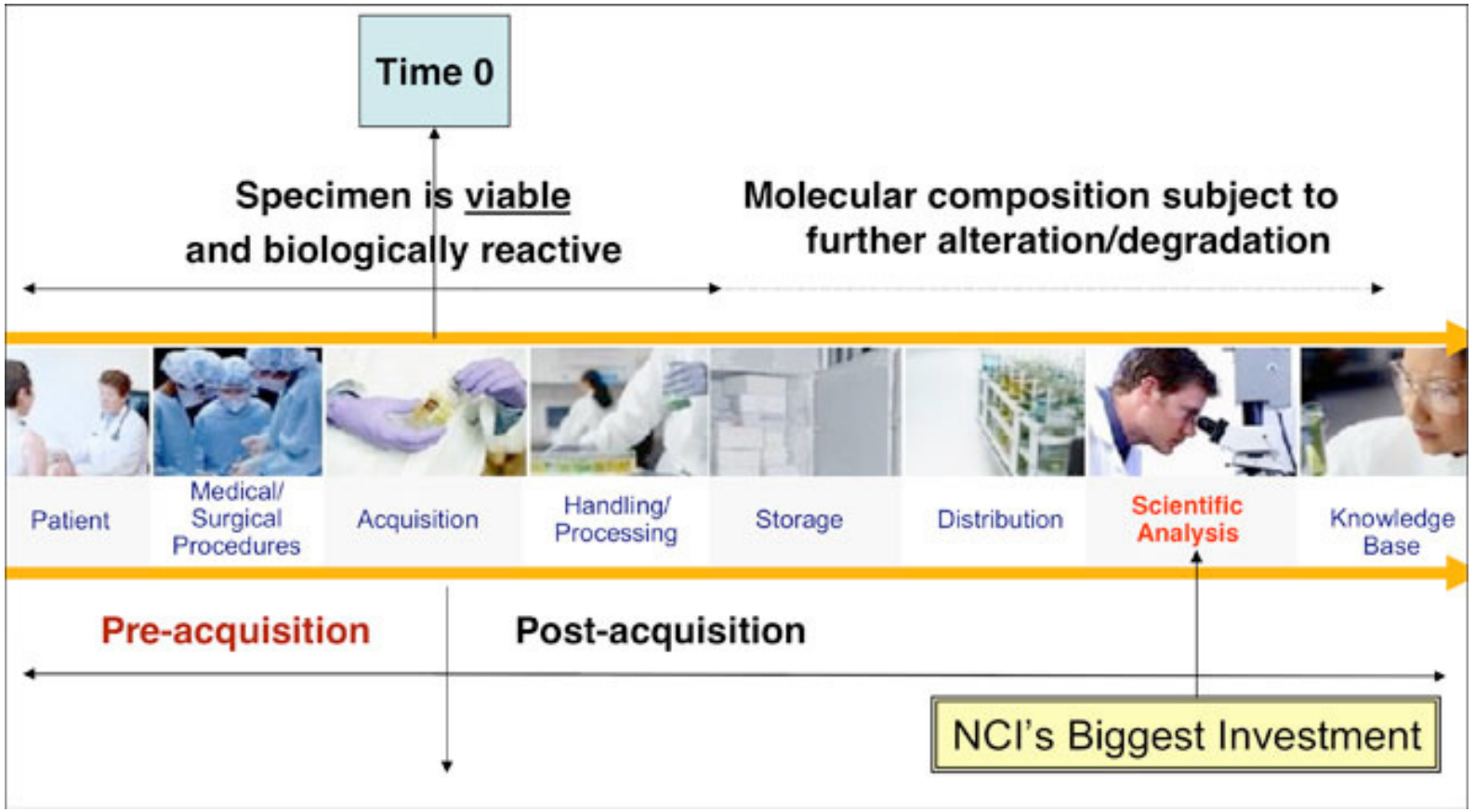
BY STEVE SILBERMAN 05.24.10 | 12:00 PM | PERMALINK

Share 0 Tweet 0 +1 3 Share Pin it

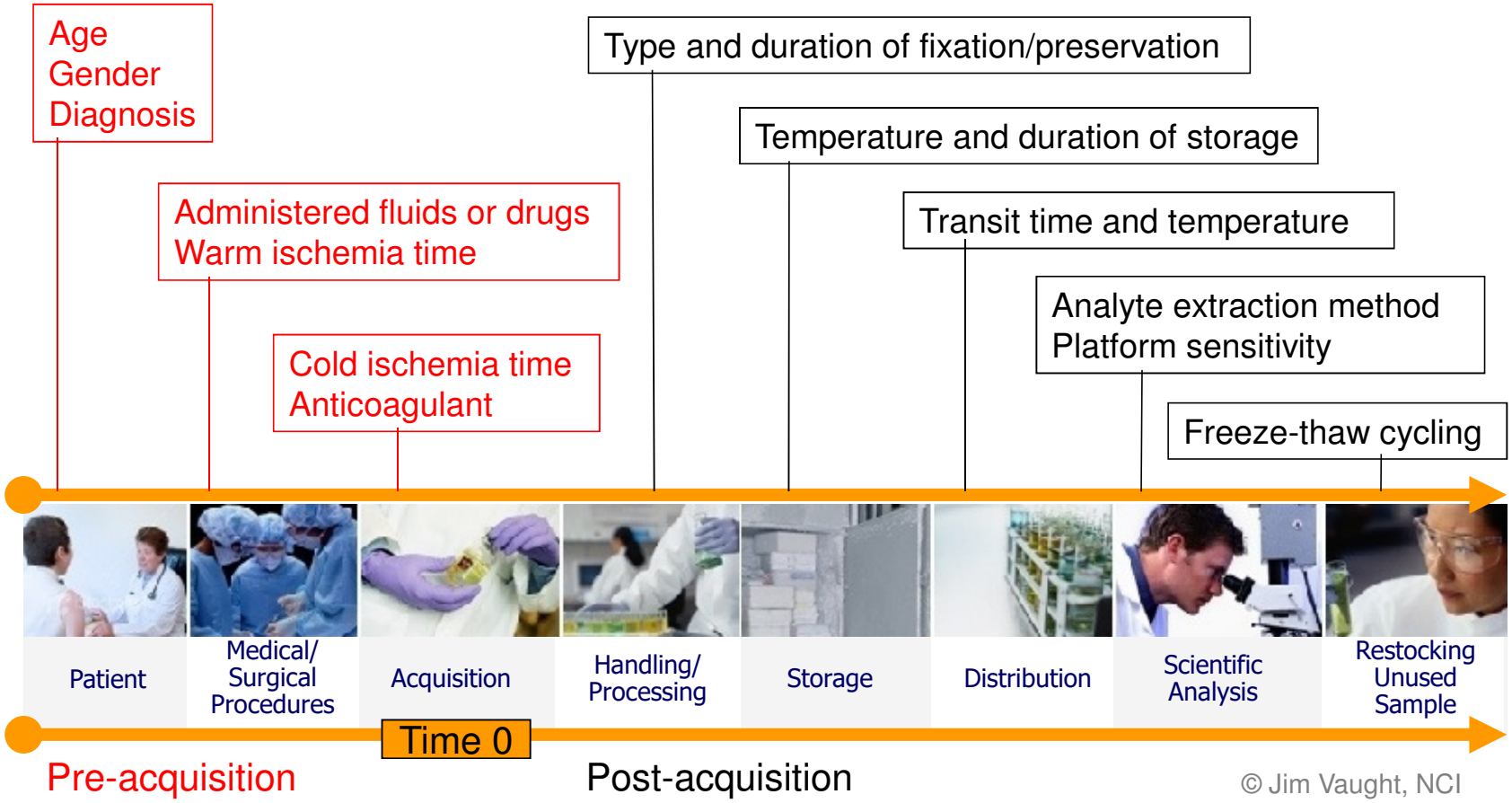


- May 2010
- 1500 glioblastoma samples for Cancer Genome Atlas
- 1 collection claimed for 12 000 samples of which ONLY 18 were acceptable
  - Traceability
  - Origin
  - ELSI
- Fitness-for-Purpose!

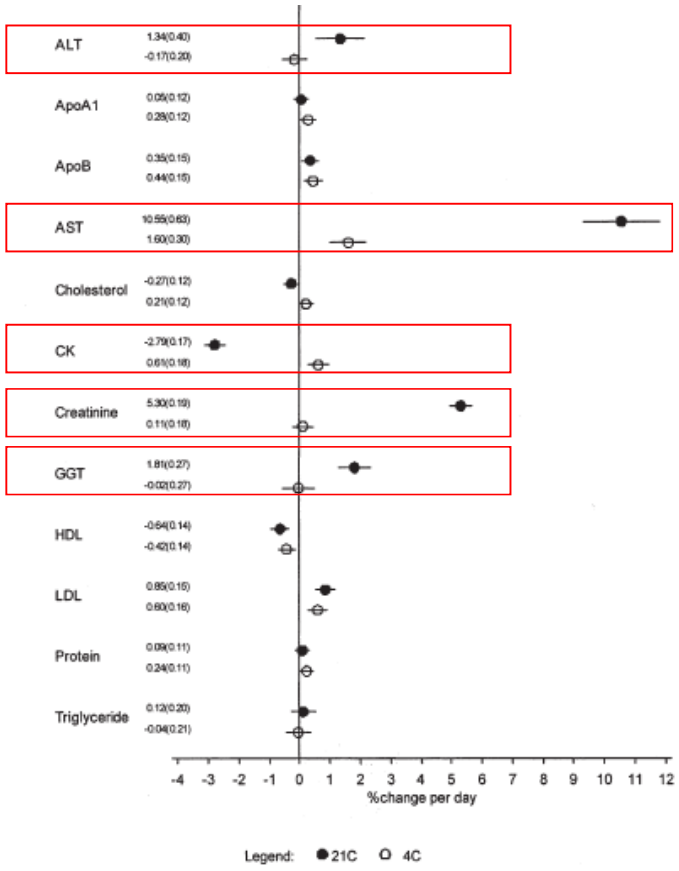
Sample Lifecycle

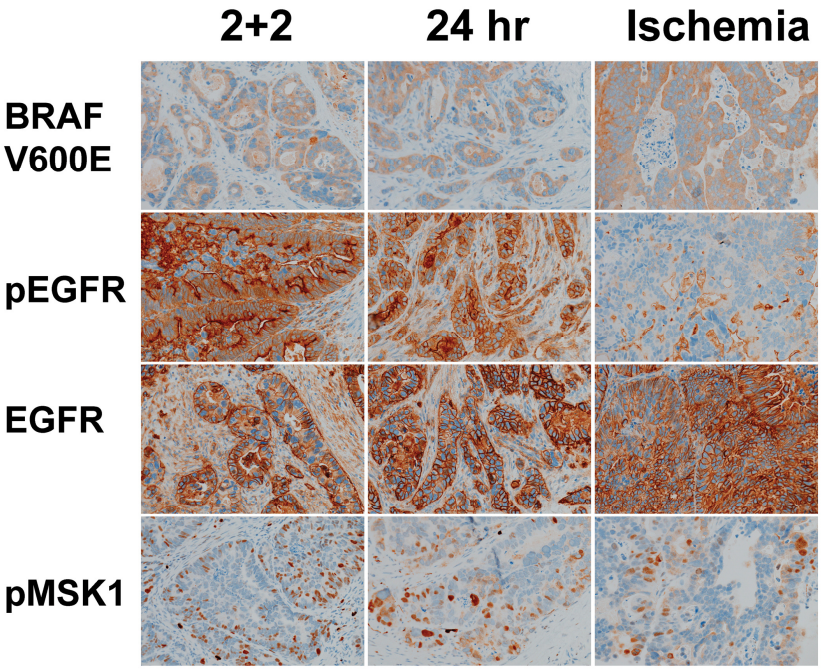


What can affect sample quality?



Impact of pre-analytical variables

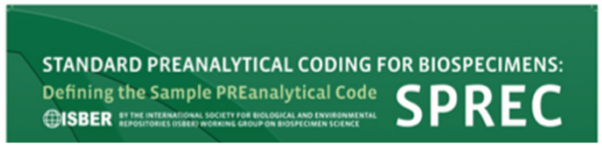


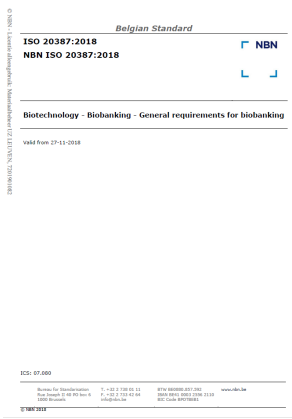


Theiss et al, 2014

How to control?

- Impossible!
  - Minimize damage with good study setup AND
- Standardization!
  - Standard PRE-analytical Code (SPREC)
  - CEN Technical Specifications for in vitro molecular examinations
  - Biobank ISO norm, guidelines and best practices
- Not only pre-analytics affect sample quality!
  - Number of freeze/thaw cycles
  - Storage/fixation duration
  - Sample processing procedures
  - Ethical, legal, societal issues (ELSI)
  - Linked data (verification) > (FBN/ISBER/OECD/BVT/MIABIS) minimal datasets
    - Biobank, Donor, Sample, … data




Belgian Standard

ISO 20387:2018

NBN ISO 20387:2018

NBN

Biotechnology - Biobanking - General requirements for biobanking

Valid from 27-11-2018

ICS: 07.080


QMS
QC
QA
Module 2
Governance
Module 3
Ethics, Privacy and Security
Module 4
Facility Design and Safety
Module 5
Quality Management and Process Improvement
Module 6
Informed Consent
Module 7
Biospecimen Collection and Processing
Module 8
Biospecimen Storage and Distribution
Module 9
Data Systems and Records Management
Module 1 – The Basics of Biobanking
Condensed version of all modules – meant to highlight key issues in establishing, maintaining and accessing a biorepository

What is a biobank?

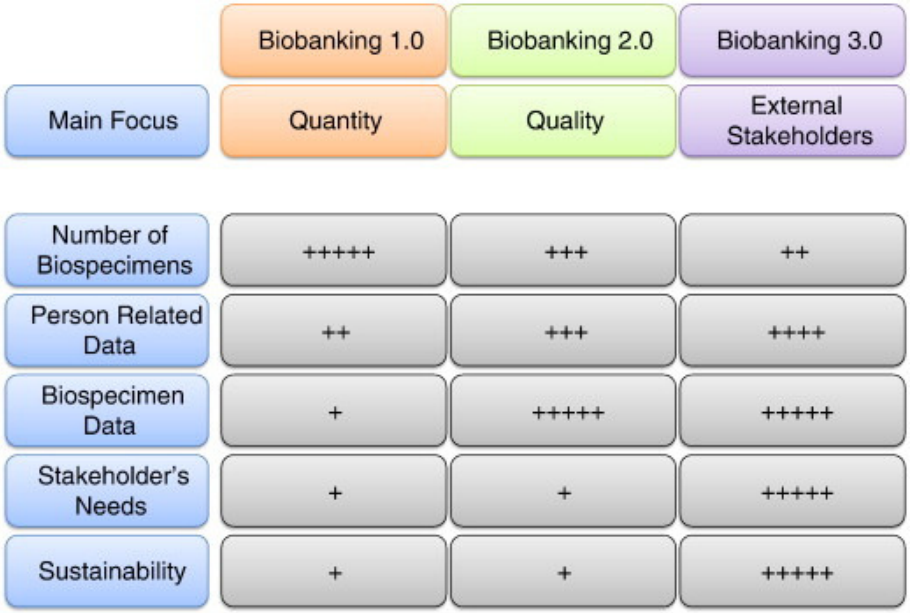
- Biobank:
  - Structured facility for (human) bodily material (personnel, infrastructure,…)
  - Receives, (processes,) stores and distributes biospecimens
  - Coupled to well documented (clinical) data
  - Can hold different collections of human bodily material
  - Quality guarantee
  - Access point to other biobanks/collections/researchers
  - Knowledge hub

- Scientific Biobank vs cell- and tissuebank:
  for scientific research, NO therapeutic purpose!

Professional biobanking

- Sample (& data) quality is assured & garantueed in long term
  - Within biobank
  - Across biobanks in a network
    - Flemish Biobank Network
    - BBMRI.be
    - Belgian Virtual Tumorbank (BVT)
    - BBMRI-ERIC

- Trusted party for your samples
  - Quality perspective
  - Professionalisation



Simeon-Dubach et al, 2014

Why is biobanking suddenly important?

- Sample quality
- Legal aspects & consequences

Legal framework human bodily material

- Law regarding patients' rights - 22AUG2002
- Law regarding experiments on man – 7MAY2004 ("experimentenwet")
- Law regarding protection of natural persons related to processing of personal data - 30JUL2018 (~GDPR)
- Law regarding acquisition and use of human bodily material (HBM) - 19DEC2008
  - Clinical application on man
  - Scientific research - RD 09JAN2018
    - **ACTIVE as of 1NOV2018**

Intention of biobank law related to research

- Protection of donor and donor's rights
  - Specific conditions for collection and/or use of HBM for scientific research
  - Donor has right to be informed when clinically relevant and validated information is available at his/her individual level.
  - Privacy (GDPR)

- Prevention of fraudulent collection and/or use of HBM
  - HBM should be traceable and identifiable at every stage of the process, from acquisition to distribution/use, during processing, auditing and storage

Legal definitions

- **Human bodily material (HBM):** any biological material, including human tissues and cells, gametes, embryos, fetuses, as well as the substances derived therefrom, whatever their degree of processing/transformation (DNA, RNA, proteins, …) (including – commercial – cell lines and stool!)

- **Biobank:** the structure that, for the purposes of scientific research excluding research with a medical application to humans, obtains human body material (HBM), where appropriate, processes, stores and makes available, as well as, where applicable, the data relating to human tissue material and the donor.

Types of research use of HBM

- **Primary use:** any use as consented to by the donor at the time of procurement

  INFORMED CONSENT

- **Secondary use :** (on remaining material) any other use than consented to by donor at time of procurement

  INFORMED CONSENT (reconsent, EC waiver, clause in primary IC)

- **Residuary material:** HBM procured for diagnostic or treatment purposes that is no longer necessary and therefore can be destroyed, provided a sufficient sample is kept for setting, finetuning or finalizing the diagnosis or treatment

  PRESUMED CONSENT/OPT OUT

! residuary material (residuair materiaal) ≠ remaining material (overblijvend materiaal)

Consequences for research on HBM

- HBM for research has to be obtained from a NOTIFIED biobank
  - Applicable to any primary sample collection/secondary use/ use of diagnostic HBM/import of foreign HBM/…
  - Written agreement between biobank and end user

- HBM for research imported into or exported outside of Belgium must be registrered in a Belgian biobank (same rules apply)
  - proof that samples have been taken according to local legislation and according to international ethical/privacy/personal data standards

- HBM can only be collected by certain qualified health professionals (supervision by doctor/dentist) in a safe environment

Biobank law – biobank responsibilities

- Appoint a biobank manager (medical doctor)
- Obtain and maintain EC approval for goals and activities (bi-annual evaluation)
- Be notified to the FAMPH
- Ensure traceability:
  - Unique identification of material
  - Registry of sample movements available to FAMHP
- Oversee donor's consent: verify content of informed consent before provision of samples to researcher
- Written agreement with end-user (researcher)
  - Specific subject of the scientific research
  - Responsibilities of end-user to ensure traceability
  - End-user's technical and organizational measures to protect privacy if personal data are provided and to return meaningful information

Ethics: ownership vs. custodianship of HBM

- Different people/entities are involved with HBM for research use:
  - Patients,
  - the physician/department/care programme physically obtaining the HBM and/or performing the diagnosis on the HBM (if applicable) and/or making therapeutic use of the HBM,
  - the PI obtaining the HBM for primary use,
  - the scientist/researcher making use of the HBM outside of the clinical care path (in UZ Leuven, KU Leuven or outside this legal entity),
  - the UZ KU Leuven Biobank and the responsible administrator UZ Leuven as intended in article 2,28° of the Belgian law on HBM,
  - the CEO of UZ Leuven, ...

- None of these individuals can claim exclusive ownership/custody of the HBM.
  All are, at one point or another, responsible for some aspects of the chain of HBM. It was therefore decided and validated that the custodianship of HBM lies with a single entity, i.e. the UZ Leuven.

UZ KU Leuven approach

1. **One sole notified biobank** for the Leuven Health Science Campus
2. Studies collecting/using HBM for research require biobank approval prior to EC submission/approval
    1. Oversee donor's consent
    2. Written agreement biobank – end-user
3. HBM to be registered in Biobank Registry
    1. Proof: HBM for research obtained from notified biobank
    2. Oversee donor's consent
    3. Bi-annual report
    4. Registry available to FAMHP
4. HBM to be stored in central facility (ON4)
5. Costs
6. Access policy
7. Handling of HBM

1. One sole notified biobank – VISION/MISSION

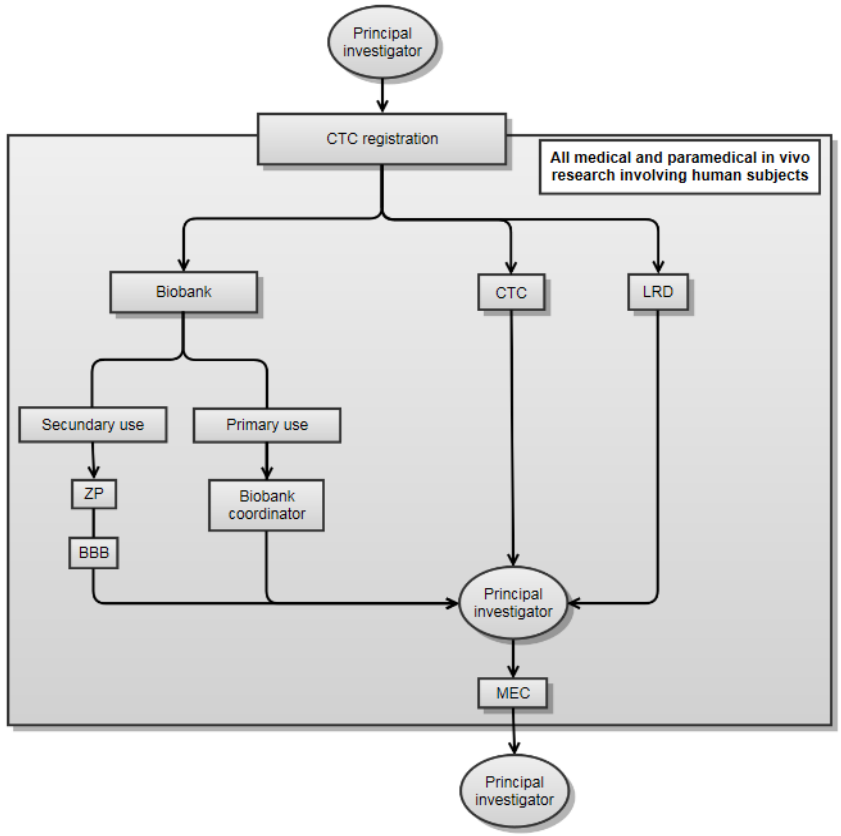
- From a quality and service oriented perspective
  - Facilitate translational research to improve public health
  - Protect stakeholders' interests (donors, researchers, UZ/KUL, FAMHP, ...)
  - Be a knowledge hub for all things biobanking

- Currently focussed on storage solutions
- In future:
  - Sample processing & QC
  - Integration in existing (clinical) sample flows

1. One sole notified biobank

- °2007
- BB manager: prof. Dr N. Ectors
- Complies to relevant (inter)national legislation (EC approval, FAMHP notification)
- Operates according to a quality management system (~ISO20387, ISBER)
- Insured as legally required
- Instated an access policy (balancing interests' of custodian and sharing of material) – cfr below
- Will install a financial model (cost recovery vs research budget burden) – cfr below
- Reports bi-annually to EC (including information as registered in biobank registry)
- Is member of (inter)national biobank networks and organisations (BBMRI, ESBB, ISBER, …)

2. Biobank approval prior to EC approval



All collections/studies/projects
(& amendments)
using and/or collecting HBM
for scientific research
to be submitted and approved
by UZ KU Leuven biobank
prior to EC approval

Studies – typical flow

- CTC application
  - CTC application form -> S-number
    - Mark “biobank as supportive service” – irrespective of storage location
  - Study protocol
  - GDPR questionaire
  - https://www.uzleuven.be/clinical-trial-center/

Studies – typical flow

- CTC application (S-number)
- Biobank application
  - Form for secondary use (CTC website)
  - Form for primary use (on request/intranet)
  - Improved, combined application form in development
  - Study protocol, informed consent, MTA (if applicable), ethical declaration/approval, CTC registration form, aob
  - Scientific value, donor's rights, traceability
    - Origin, destination, fate after use, storage duration, quantities of samples and derivatives
  - https://www.uzleuven.be/nl/biobank-0 (will be regularly updated and reflect actual biobank info)
  - wbb@uzleuven.be

Secondary Use

UZ LEUVEN

Aanvraagformulier Biobank

Gelieve dit formulier volledig ingevuld elektronisch te bezorgen aan de Wetenschappelijke Biobank (wbb@uzleuven.be - tel. 016 34 27 13 of 016 34 14 82 en http://intranet/biobanking).
Dit document, ondertekend door de Coördinator, is verplicht toe te voegen bij de initiële indiening van het dossier bij de ethische commissie onderzoek UZ / KU Leuven (EC onderzoek). Dit geldt voor elke studie (ongeacht de financiering en aard van de onderzoeken).

S-nummer:

Studieprotocol nr/naam:

Geplande startdatum studie:
Naam hoofdonderzoeker UZ Leuven:
Tel: Dienst:
Naam contact (UZ studiemedewerker):
Tel.: e-mail:
Naam firma en contactpersoon:
Tel.: e-mail:
Naam CRO en contactpersoon:
Tel.: e-mail:

Gelieve een kopie van het studieprotocol , het registratieformulier CTC evenals desgevallend het Informed Consent (IC) van de aanvraag toe te voegen.

1. Welk menselijk lichaamsmateriaal zal voor deze studie worden aangewend?

☐ **Nog aan te leggen** collectie menselijk lichaamsmateriaal in het kader van de actuele studie

1. ☐ Levende donor
   ☐ Overleden donor
   ☐ Beide
2. ☐ **Primair gebruik** voor wetenschappelijk onderzoek na wegneming voor wetenschappelijk onderzoek:
   - Gelieve IC in bijlage toe te voegen

   ☐ **Secundair gebruik** voor wetenschappelijk onderzoek na wegneming voor diagnostische en/of therapeutische doeleinden (= residuair materiaal) : opting – out (KWS), geen IC nodig

   ☐ Andere:

☐ **Bestaande collectie** menselijk lichaamsmateriaal:

☐ Aangelegd door de **UZ – KU Leuven Biobank**: opting out, geen IC nodig.
☐ Aangelegd in het kader van een **vroeger wetenschappelijk project:**
☐ Het IC van initieel project dekt ook deze toepassing (gelieve toe te voegen in bijlage)
☐ Het IC van initieel project dekt deze toepassing niet:
☐ Nieuw IC (gelieve toe te voegen in bijlage)
☐ MEC toestemming voor gebruik menselijk lichaamsmateriaal zonder IC

(In geval van onmogelijkheid om de toestemming te vragen tot het secundaire gebruik, of indien deze vraag uitzonderlijk ongeëigend zou zijn, kan tot secundair gebruik worden overgegaan nadat een ethisch comité bedoeld in artikel 11, § 3, tweede lid, van de wet van 7 mei 2004 inzake experimenten op de menselijke persoon over de toepassing van dit lid en artikel 21 een positief advies heeft uitgebracht)

☐ Andere:

Is er overleg geweest met de betrokken persoon over dit materiaal:

☐ Neen
☐ Ja, naam contact:

2. Traceerbaarheid:

- **Type** menselijk lichaamsmateriaal (serum, hartweefsel, fibroblasten, ...):
- **Oorsprong** van het menselijk lichaamsmateriaal indien niet herkomstig van personen/patiënten gerekruteerd door PI maar van een derde.
  Identificatie van deze derde:
  ☐ Ziekenhuis:
  ☐ Arts:
  ☐ Biobank:
  ☐ Andere:
- **Bestemming** van het menselijk lichaamsmateriaal indien verstuurd buiten UZ Leuven:
  ☐ Ziekenhuis:
  ☐ Arts:
  ☐ Biobank:
  ☐ Andere:
- Welke afspraken bestaan er rond het **restmateriaal** na einde studie:
  ☐ Terugzending
  ☐ Vernietiging
  ☐ Andere:

- Hoeveel (aantal donoren en hoeveelheid/donor) menselijk lichaamsmateriaal
  - zal worden afgenomen:
  - is momenteel beschikbaar (in geval van bestaande collecties):
- Hoeveelheid (per staal/donor) menselijk lichaamsmateriaal noodzakelijk voor studie:

3. Indien de UZ – KU Leuven Biobank en/of de onderzoeker niet over het benodigde materiaal beschikken, mag er dan menselijk lichaamsmateriaal gebruikt worden van andere bestaande biobanken ?

☐ Neen
☐ Ja

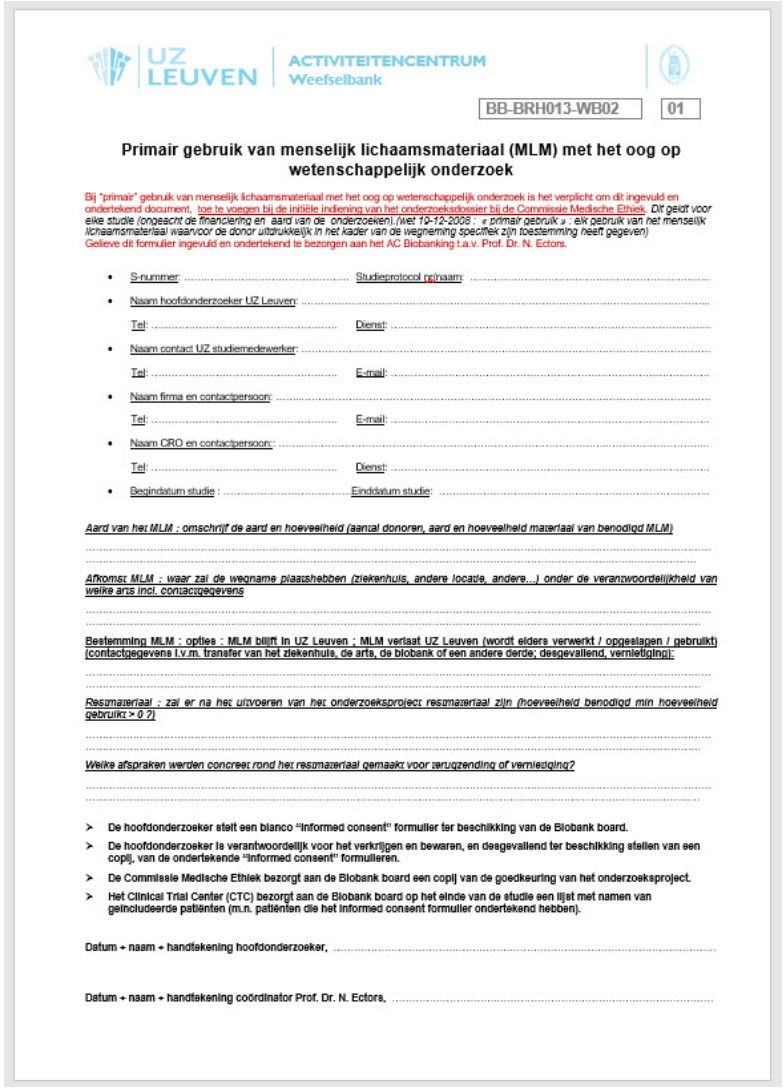
4. Is er over deze studie reeds voorafgaandelijk contact geweest met het AC Biobank ?

☐ Neen
☐ Ja, naam contact UZ – KU Leuven Biobank:

Het AC Biobank verklaart geen bezwaren te hebben tegen het voorgestelde studieprotocol.

Datum: / / **Naam:** **Handtekening:**

Primary Use



UZ LEUVEN | ACTIVITEITENCENTRUM Weefselbank

BB-BRH013-WB02 | 01

Primair gebruik van menselijk lichaamsmateriaal (MLM) met het oog op wetenschappelijk onderzoek

Bij "primair" gebruik van menselijk lichaamsmateriaal met het oog op wetenschappelijk onderzoek is het verplicht om dit ingevuld en ondertekend document, toe te voegen bij de initiële indiening van het onderzoeksdossier bij de Commissie Medische Ethiek. *Dit geldt voor elke studie (ongeacht de financiering en aard van de onderzoeken) (wet 19-12-2008 : « primair gebruik » : elk gebruik van het menselijk lichaamsmateriaal waarvoor de donor uitdrukkelijk in het kader van de wegneming specifiek zijn toestemming heeft gegeven)*
Gelieve dit formulier ingevuld en ondertekend te bezorgen aan het AC Biobanking t.a.v. Prof. Dr. N. Ectors.

- S-nummer: ..... Studieprotocol nr/naam: .....
- Naam hoofdonderzoeker UZ Leuven: .....
  Tel: ..... Dienst: .....
- Naam contact UZ studiemedewerker: .....
  Tel: ..... E-mail: .....
- Naam firma en contactpersoon: .....
  Tel: ..... E-mail: .....
- Naam CRO en contactpersoon:: .....
  Tel: ..... Dienst: .....
- Begindatum studie : ..... Einddatum studie: .....

Aard van het MLM : omschrijf de aard en hoeveelheid (aantal donoren, aard en hoeveelheid materiaal van benodigd MLM)

.....

.....

Afkomst MLM : waar zal de wegname plaatshebben (ziekenhuis, andere locatie, andere...) onder de verantwoordelijkheid van welke arts incl. contactgegevens

.....

.....

Bestemming MLM : opties : MLM blijft in UZ Leuven ; MLM verlaat UZ Leuven (wordt elders verwerkt / opgeslagen / gebruikt) (contactgegevens i.v.m. transfer van het ziekenhuis, de arts, de biobank of een andere derde; desgevallend, vernietiging):

.....

.....

Restmateriaal : zal er na het uitvoeren van het onderzoeksproject restmateriaal zijn (hoeveelheid benodigd min hoeveelheid gebruikt > 0 ?)

.....

.....

Welke afspraken werden concreet rond het restmateriaal gemaakt voor terugzending of vernietiging?

.....

.....

- De hoofdonderzoeker stelt een blanco "informed consent" formulier ter beschikking van de Biobank board.
- De hoofdonderzoeker is verantwoordelijk voor het verkrijgen en bewaren, en desgevallend ter beschikking stellen van een copij, van de ondertekende "informed consent" formulieren.
- De Commissie Medische Ethiek bezorgt aan de Biobank board een copij van de goedkeuring van het onderzoeksproject.
- Het Clinical Trial Center (CTC) bezorgt aan de Biobank board op het einde van de studie een lijst met namen van geïncludeerde patiënten (m.n. patiënten die het informed consent formulier ondertekend hebben).

Datum + naam + handtekening hoofdonderzoeker, ...

Datum + naam + handtekening coördinator Prof. Dr. N. Ectors, ...

Under construction

Please submit this fully completed form electronically to the Scientific Biobank (wbb@uzleuven.be - tel. 016 34 56 69). This document, signed by the Coordinator, is required to be enclosed with the initial submission of the file to the Medical Ethics Committee. This applies to every study (regardless of the funding and/or the financing and nature of the study). More info regarding the Biobank application at http: // intranet / biobanking (only for UZ Leuven employees).

S-number: S S-number

Studieprotocol nr/naam: Title

Expected start date study: Date — Expected end date study: Date

Name principal investigator UZ Leuven: Name

Tel: Phone PI — e-mail: Email

Dienst: Department

Name contact (UZ study coordinator): Name

Tel.: phone — e-mail: Email

Name Sponsor and contact person: Name

Tel.: phone — e-mail: Email

Name CRO and contact person: Name

Tel.: Phone — e-mail: Email

1. Study Details

Expected date at which the first sample will be collected: Sampling start date ☐ NVT

Expected date at which the last sample will be collected: Sampling stop date ☐ NVT

Monocentric/multicentric: *Select mono-/multicentric*

Academic/commercial: *Select academic/commercial*

2. Biobank application type

Indicate which of the following categories apply to the concerning research project. Multiple answers are possible. Please complete the sections of the application form, indicated in the table below, for each applicable application type[1].

Application type	Section
☐ Primary Use	Complete section 3
☐ Setup a collection - Primary Use (umbrella)	Complete section 3
☐ Setup a collection - Residuary Material (umbrella)	Complete section 4
☐ Secondary Use of human bodily material (HBM) remaining after Primary Use	Complete section 4
☐ Secondary Use of Residuary Material	Complete section 4
☐ Production of cell lines from Primary Use	Complete section 3
☐ Production of cell lines from secondary Use	Complete section 4
☐ Use of established cell lines	Complete section 5
☐ Import – with the intention to setup of collection of HBM	Complete section 3/4
☐ Import – with the sole intention to perform sample analysis and return the results to the sender	Complete section 3
☐ Export	Complete section 3
☐ Clinical trial [2]	Complete section 6
☐ Clinical trial with optional additional/left-over material for future use	Complete section 6, (3/4)

[1] For detailed information on the application types, please refer to section 11 of this form.
2 "clinische proef", as defined in Art. 2, 7° of the Law on experiments on human people dd 7-05-2004

3. HBM - Primary use

Please complete the following sections for all HBM that is part of the current application and for which the donor has explicitly and specifically given written consent in the context of the removal, storage and/or use of the material subsequent to being informed about all aspects of the research project to which this appertains

3.1. Origin of the HBM

List all samples that will be collected using the table below. Complete one tier per sample type. Indicate the sample origin as well as the collected quantities.

Type of HBM	Origin/collection site	Quantity
	☐All info equal to 1st tier	☐All info equal to 1st tier
HBM type: HBM type	Select origin Name institution: Institution Address: Address HBM transfer agreement available: ☐ Yes ☐ No	Number of donors: ### Number of time points: ### Samples/donor/time point: ### Quantity/sample: ### Unit Total quantity/per donor: ###

To add an additional sample type, please click on the table and select the ⊞ sign which will become visible at the bottom right corner of the table.

3.2. Processing and storage of HBM

Please list all derivatives obtained from the samples mentioned above in the table below. Indicate where these samples will be stored, for which period of time and at which condition as well as the intended quantities that will be obtained per derivative type. Complete the shipment details if you intend to store/analyze these samples at a site other than UZ/KU Leuven.

Type of HBM	Quantity	Storage	Shipment
	☐All info equal to 1st tier	☐All info equal to 1st tier	☐All info equal to 1st tier
Parent sample: Enter HBM type	Number of aliquots/parent [4]: ###	Condition: Select condition Name institution: Institution	Samples shipped: ☐ Yes ☐ No Consignee Name: Consignee
Derivative Enter HBM type ☐ no derivatives obtained[3]	Aliquot quantity: ### Unit	Address: Address Period (years): ###	Consignee phone: Phone Consignee Email: Email HBM transfer agreement: ☐ Yes ☐ No

To add an additional sample type, please click on the table and select the ⊞ sign which will become visible at the bottom right corner of the table.

3.3. Use of HBM

Indicate the intended sample usage in the table below.

Type of HBM	Sample use
	☐All info equal to 1st tier
HBM type	Quantity immediately used within project without biobank storage: ### samples Quantity stored for future use within this project: ### *samples* Quantity stored for future use outside the scope of this project: ### samples

To add an additional sample type, please click on the table and select the ⊞ sign which will become visible at the bottom right corner of the table.

3.4. Destination of remaining material

Clarify what will happen to the samples after the study has been completed

Type of HBM	Destination of remaining material	
	☐All info equal to 1st tier	☐All info equal to 1st tier
HBM type	Select destination of left-over material,	If stored: Name institution:Institution Address:Address Period (years): ###

To add an additional sample type, please click on the table and select the ⊞ sign which will become visible at the bottom right corner of the table.

[3] *Check this box if no further processing steps occur prior to sample storage.*
[4] *Enter "0" in case no aliquots will be obtained from the sample.*

8. Documents

In order to allow the UZ/KU Leuven biobank to make an informed assessment of the content of the research project we ask you to include the following documents with your application, if available:

- Protocol
- Lab manual
- Informed consent template
- CTC application form
- EC approval[10]/waiver
- Ethical declaration of the vendor of cell lines
- HBM transfer agreement

9. Terms and conditions

The principle investigator:

- confirms that the data provided in this application form is complete and correct.
- confirms that the collection, processing, storage and use of the HBM within the context of this research project will remain limited to what is described within this application form and the accompanying study documents.
- agrees to comply with all provisions regarding traceability as described in Article 22 of the Belgian law on Human Body Material dd. 19-12-2008.
- agrees that the collection of the HBM occurs in accordance with art. 2 of the royal decree on biobanking dd.05-02-2018.
- agrees that, in case that art. 11 of the Belgian law on Human Body Material dd.19-12-2008 applies, any feedback, in the event that sample analyses generates information that has a significant impact on the donor's health status, will be communicated to the donor of the concerning sample.
- agrees to provide the minimal dataset required to register the HBM into the UZ/KU Leuven biobank registry as described by annex BB-TEC002-AN01.
- confirms that all required technical and organisational measures are in place in order to guaranty the protection of the donor's personal data in accordance with the provisions stated in EU regulation 2016/679 and the Belgian law on the protection of natural persons with regard to the processing of personal data dd 30 July 2018.
- agrees to notify the biobank of any substantial amendments that affect the biobanking aspects of the research project.

10. Approval

Signature Principle Investigator	Signature Biobank Coordinator
Name:	Name:
Date:	Date:
Signature:	Signature:

[10]: *Not applicable in case of primary use with the exception of applications in the context of the rectification of research projects not submitted to the biobank in the past.*

Protocol & ICF content

	Application form BB	Study protocol	ICF
Which HBM	+	+	+
Amount/sample	+	+	+
# samples / donor	+	+	+
# donors	+	+	nvt
Donor type	+	+	nvt
Retention period	+	+	+
Retention location	+	+	+
Shipment Yes/No	+	+	+
Destination/fate after use (destruction; return; ext storage)	+	+	+
progeny: UZ – KUL – external (ZH – BB – MD)	+	+	nvt
Import / export	+	+	+(*)
Future Use	+	+	+(*)
Commercial use?	+/-?	+/-?	+(*)
Privacy/GDPR	-	+	+(*)

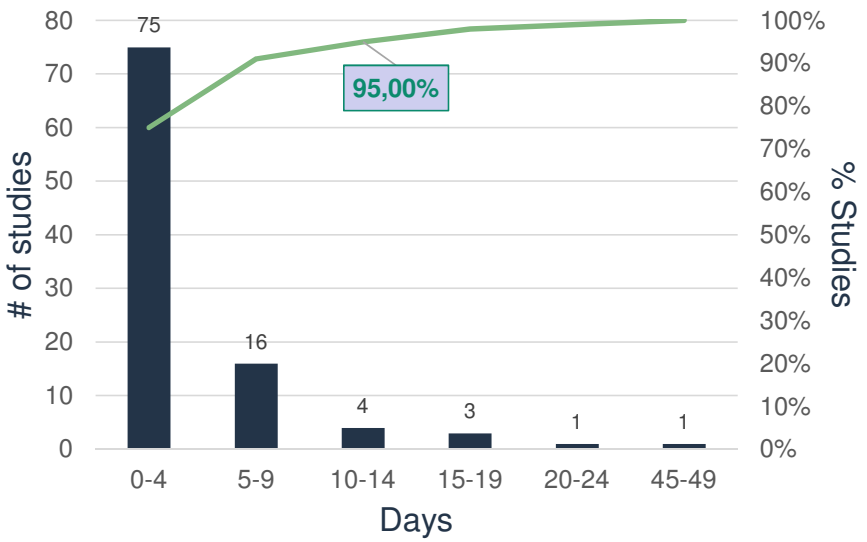
(*) template clauses available/in development

Studies – typical flow

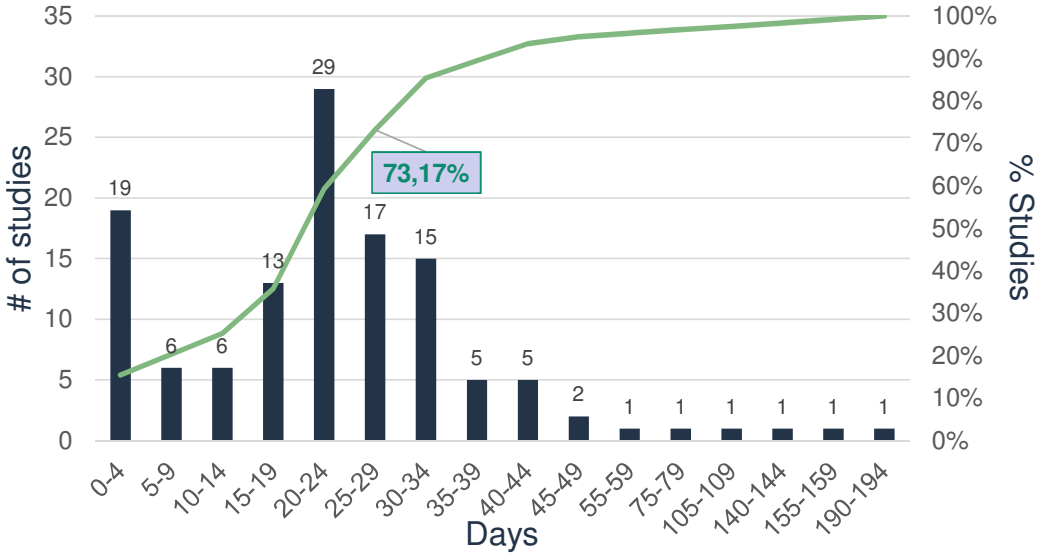
- CTC application (S-number)
- Biobank application
  - Administrative check
    - Biobank aspect/content ICF
    - Consensus regarding HBM between ICF, study protocol and biobank application form
    - Relevant documentation present for the related case (eg original ICF for SU, MTA et al for import, ...)
  - Admissible file
    - PU -> BB manager for approval (dT: 1-2w)
    - SU -> 2 BB Board readers & related care program(s) (dT: 4w)
    - Insuperable issues -> discussed at BB Board

Evaluation procedure – Turn Around Time*

Primary use



Secundary use**



*** Secundary use exclusively or in combination with primary use*

** Number of days until study approval, starting from an admissible file*

Studies – typical flow

- CTC application (S-number)
- Biobank application
- EC application*
  - https://www.uzleuven.be/nl/ethische-commissie/onderzoek
  - Study protocol, informed consent, BB approval, aob

- Amendments!
  - Impact on HBM aspect of study -> BB aproval

3. HBM to be registered in Biobank Registry

- Legal obligation: traceability & basis for (continued) EC approval
- Registration of sample movements enabling HBM for research
  - incoming (i.e. collection, processing, transformation)
  - outgoing (i.e. use)
- Serves as central registry for FAMHP
- Communication to FAMHP through Biobank Manager UZ/KU Leuven Biobank (NE)
- In case of FAMHP inspection/questions, the Biobank Manager can contact PI regarding content of the Registry

- Biobank will perform internal audits to verify conformance

Biobank Registry UZ / KU Leuven

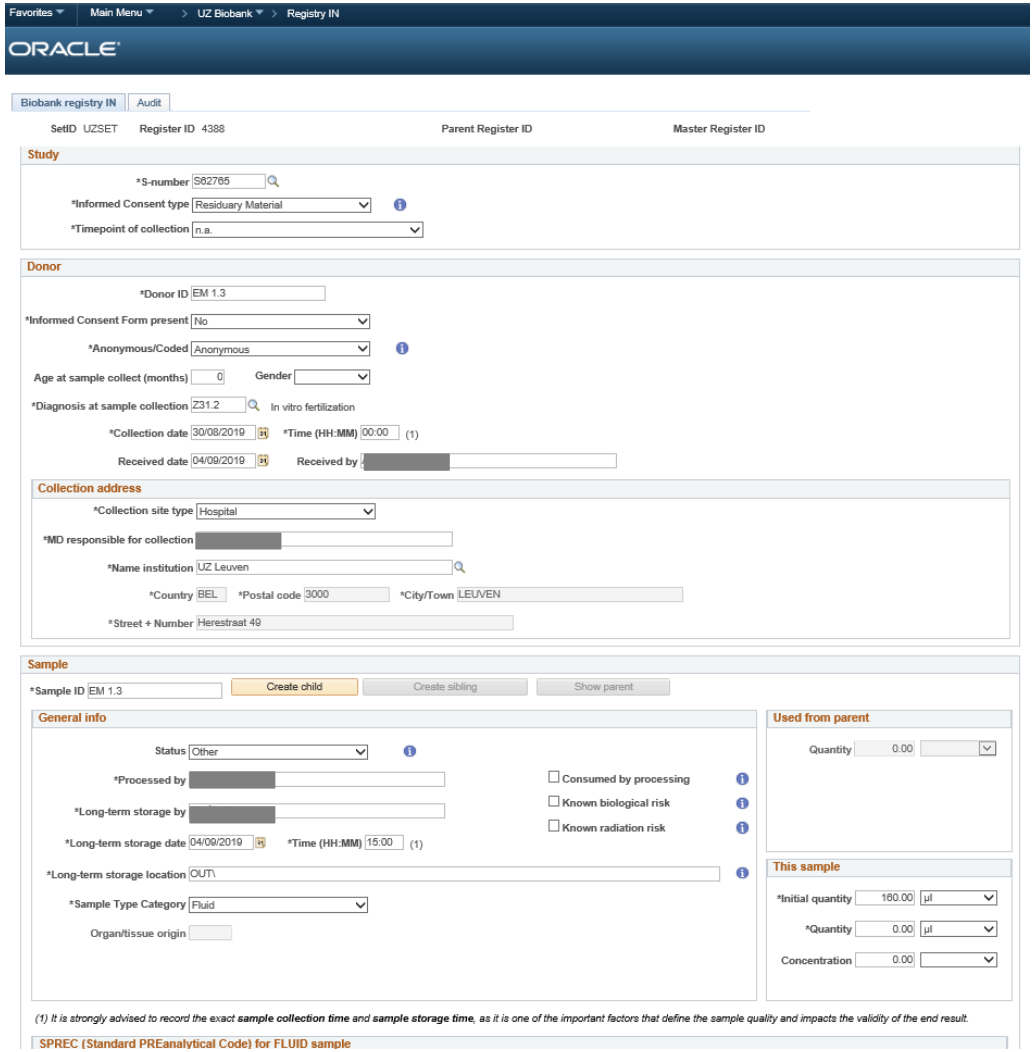
- Application in peoplesoft logistiek (UZLeuven)
  - Temporary solution in attendance of SPECTRA (IT UZ Leuven development)
- Access requested through form BB-GEN022-FO01
  - BBB and EC approved studies (S number)
  - External access possible for non-UZ users
- Consensus: every container (irrespective of amount of fragments inside) has a unique ID to guarantee traceability
  - eg 5 tubes of 500 µl serum = 5 IDs
  - eg 1 tube holding 5 biopsies = 1 ID
- All collected samples and processed samples shall be registered
- Accuracy of registration of sample movements enabling HBM for research is responsibility of PI/medical chief and his/her team
- 14d registration delay allowed

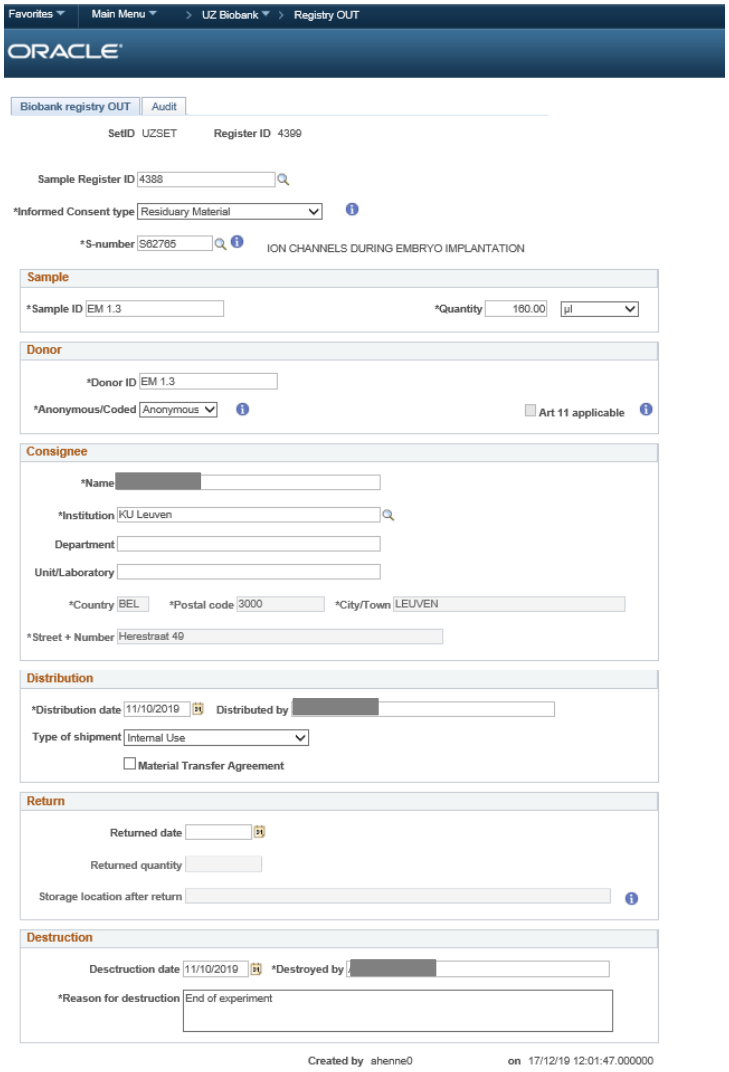
Biobank Registry

- Minimal Dataset (MDS) constructed based on
  - Legal requirements
  - Operational requirements (eg volumes)
  - (Inter)national Biobank quality standards (eg MIABIS, FAIR data)
  - MDS Flemish biobank network
  - Standard Pre-analytical Code (SPREC)

  - Cell line specific dataset in development
  - “live” storage (PDX models, sustained cell line culture, ...)

Biobank Registry Peoplesoft – IN vs OUT





Biobank Registry Peoplesoft - IMPORT

- Two approaches for data input:
  - Through the user interface
  - Through excel upload

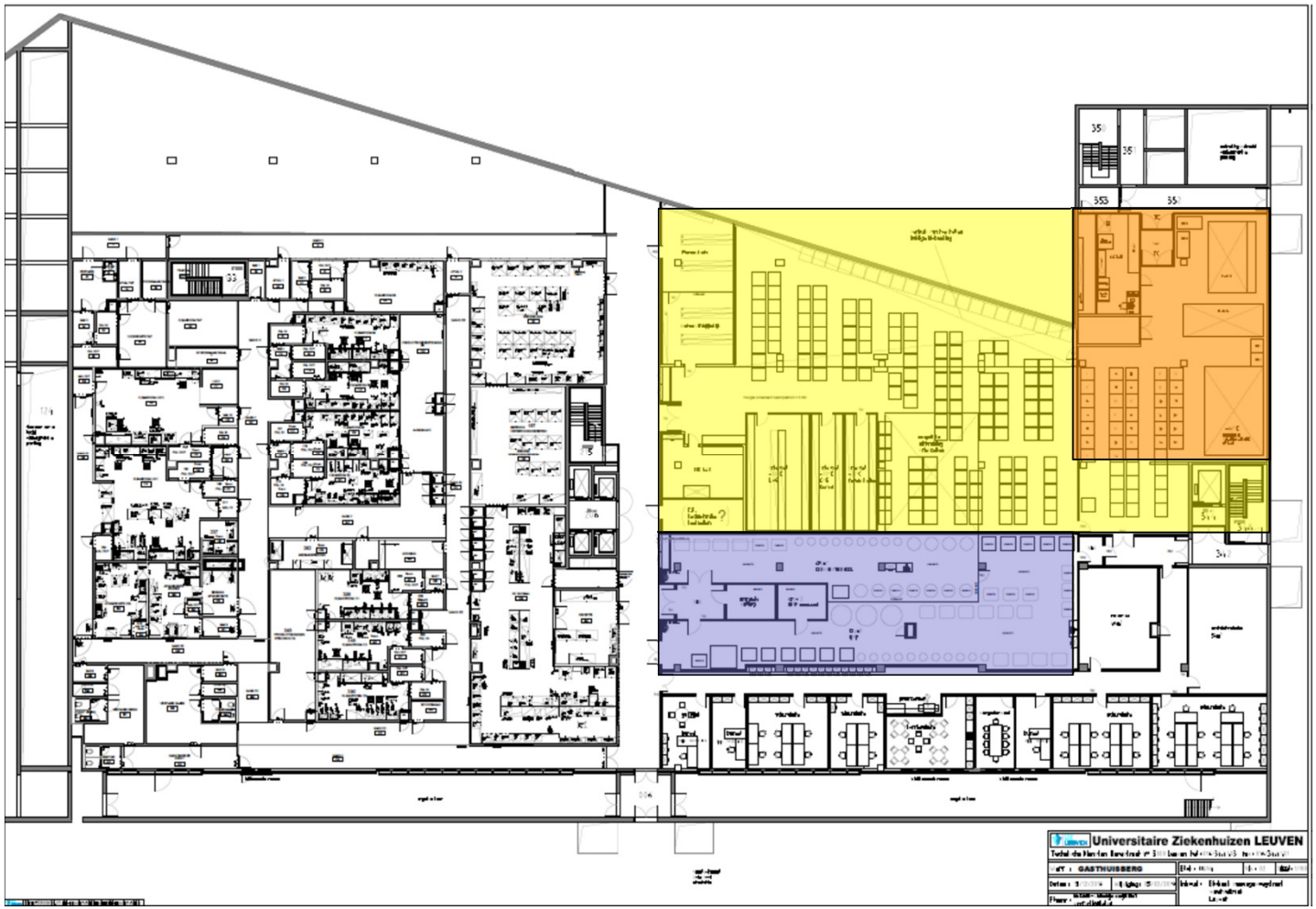
- Database/inventory system already in use at researchers'

- Template for data upload via excel file for Registry IN and OUT
  - Data to be registered by research team and to be provided to biobank in fixed format
  - Initial uploads by BB -> when successful by research team
  - Excel template IN: BB-TEC002-FO01 Template biobank_reg_in
  - Excel template OUT: BB-TEC002-FO02 Template biobank_reg_out

4. HBM to be stored in central facility

- All HBM stored on the Leuven Health Science Campus:
  - Stored in extended centralized storage facility (ON4 – 2nd floor)
  - Anticipated due date OCT2020 (mechanical storage)
    - LN2 facility – early 2021
    - FFPE/formaldehyde – pathology territory (log platform), biobank management
  - De-central storage for samples is allowed by agreed exception only
    -> still under custodianship of UZ KU Leuven Biobank
    -> certain conditions apply
  - As soon as generated (14d transfer delay allowed)

UZ LEUVEN



“2019 -2022” ON4 niv 02+ 03

Offer

- Access controlled facility
  - Form BB-GEN011-AN03-V1 Code of Conduct Biobank Facility
  - Form BB-GEN011-AN05-V1 Access Request Form
- Real-time temperature monitoring
  - Regular trend analysis -> preventive approach
- Independent dual alarm monitoring
- Technical oversight & operations through biobank
- Repair/replacement and temporary back-up device costs at biobanks' expense

Storage solutions provided

- Floor space: place existing storage equipment on biobank floor
- Storage equipment: biobank provides equipment to store your HBM
  - Option: content management by user or by biobank
- Automated storage:
  - Content management by biobank
  - Compatible vials
  - Storage at -20°C or at -80°C

Automated Sample Stores @ UZLeuven

- Labstore I (-20°C)
  - Content: +/- 700 000 tubes
  - Pick times:
    - 1 tube: 2 min
    - 10 tubes: 2 min
    - 100 tubes: 6 min
    - 1000 tubes: 33 min
- Biostore (-80°C)
  - Content: +/- 600 000 tubes
  - Pick times:
    - 1 tube: 4 min
    - 10 tubes: 4 min
    - 100 tubes: 9 min
    - 1000 tubes: 91 min

Fit for purpose storage

- Labelling
  - GDPR compliant (no initials, date of birth, no EA/MD, etc)
  - Indelible/permanent
- Storage containers
  - Fit for purpose: no eppendorf tubes for long-term storage!!!

5. Costs

PRICELIST BIOBANKING UZLEUVEN	REAL COST	COMMERCIAL STUDY	COMMERCIAL STUDY	NON-COMMERCIAL	NON-COMMERCIAL
MANAGEMENT					
Biobank agreement, start-up, administration Quality, certification, accreditation, audit, regulatory issues	200 € / study	300 € / study		100 € / study	
Storage IN (=Intake)		**tasks performed by PI**	**tasks performed by BB**	**tasks performed by PI**	**tasks performed by BB**
Conditioning of sample prior storage : centrifugation incl. labelling	1 € / sample	NO COST	1,5 € / sample	NO COST	1 € / sample
Conditioning of sample prior storage : Aliquoting into cryotubes/standaard tubes incl. labelling	1,25 € / cryotube	NO COST	1,5 € /cryotube	NO COST	1 € / cryotube
Conditioning of sample prior storage : others		TBD	TBD	TBD	TBD
Placing into "automated" storage (includes provision by biobank of cryotubes used for placing samples into "automated" storage)	2 € / sample	NA	2,5 € / sample	NA	1 € / sample
Placing into "manual" storage	2 € / sample	NO COST	2,5 € / sample	NO COST	1 € / sample
Collection of data related to biological specimens (Biobank registry = mandatory)		**tasks performed by PI**	**tasks performed by BB**	**tasks performed by PI**	**tasks performed by BB**
Direct registration of data into Biobank Registry of UZ KU Leuven is mandatory		NO COST	NA	NO COST	NA
Storage					
SAMPLE CONTAINER VOLUME : large - Primary tube (-80°C / -20° / 4°) in manual storage	0,5 € / year	0,5 € / year		0,2 € / year	
SAMPLE CONTAINER VOLUME : small (< 2 ml) - Cryo tube or standard tube (-80°C / -20°C) independent of storage type (automated / manual)	0,2 € / year	0,2 € / year		0,1 € / year	
Tissue Paraffin (RT)	0,1 € / year	0,1 €/ year		0,05 €/ year	
Tissue slide (RT)	0,05 € /year	0,05 €/ year		0,02 €/ year	
Liquid nitrogen	0,5 € / year	0,5 €/ year		0,2 €/ year	
Storage OUT (=Withdrawal)		**tasks performed by PI**	**tasks performed by BB**	**tasks performed by PI**	**tasks performed by BB**
Picking of individual tubes/samples from "manual" storage	2,5 € /sample	NO COST	3,5 € /sample	NO COST	2 € / sample
Picking of individual tubes/samples from "automated" storage	2,5 € /sample	NA	3,5 € /sample	NA	1 € / sample
Conditioning post storage - aliquoting into cryotubes/standard tubes incl. labelling	1,25 € / cryotube	NO COST	NO COST	NO COST	1 € / cryotube
Packaging for transport incl. dry ice	real cost	NO COST	TBD - courier	NO COST	TBD - courier
Transport	real cost	NO COST	TBD - courier	NO COST	TBD - courier
Others : collaboration with UZLeuven Extraction Facility		https://www.uzleuven.be/en/centre-for-human-genetics			
Others : collaboration with "Pathology Lab UZLeuven"		https://www.uzleuven.be/en/pathology			

Definition sample :

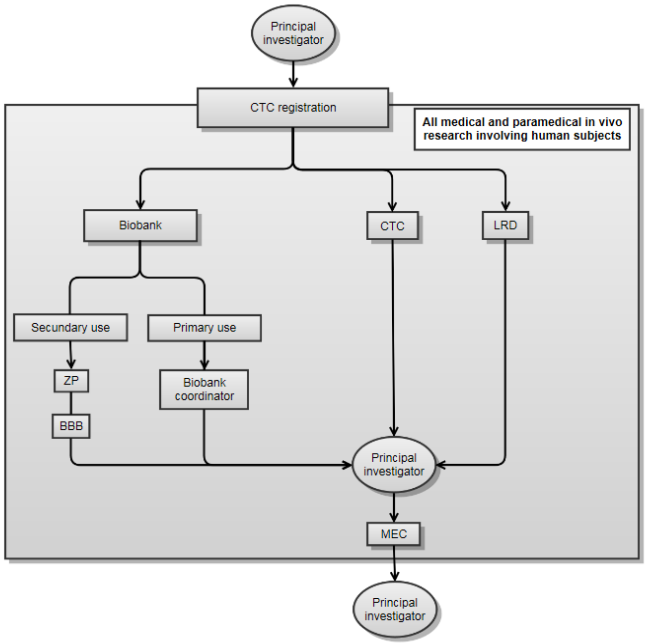
sample of human body material : any biological body material , including human tissues and cells, gametes, embryos, fetuses, as well as the substances extracted from it, independently of their degree of processing ; tissue, blood, serum, tissue slide, paraffin slide ... defined as one individual storage container/item/vessel

Definition commercial vs. non-commercial :

commercial (investigator/sponsor = pharmaceutical company) vs. non-commercial (investigator/sponsor = academic institution or FWO/FNRS) studies ; "as determined in the CTC application form of the study" ; request form (http://wiki/display/ctc/Opstarten+studie)

PI = principal investigator

6. Access policy

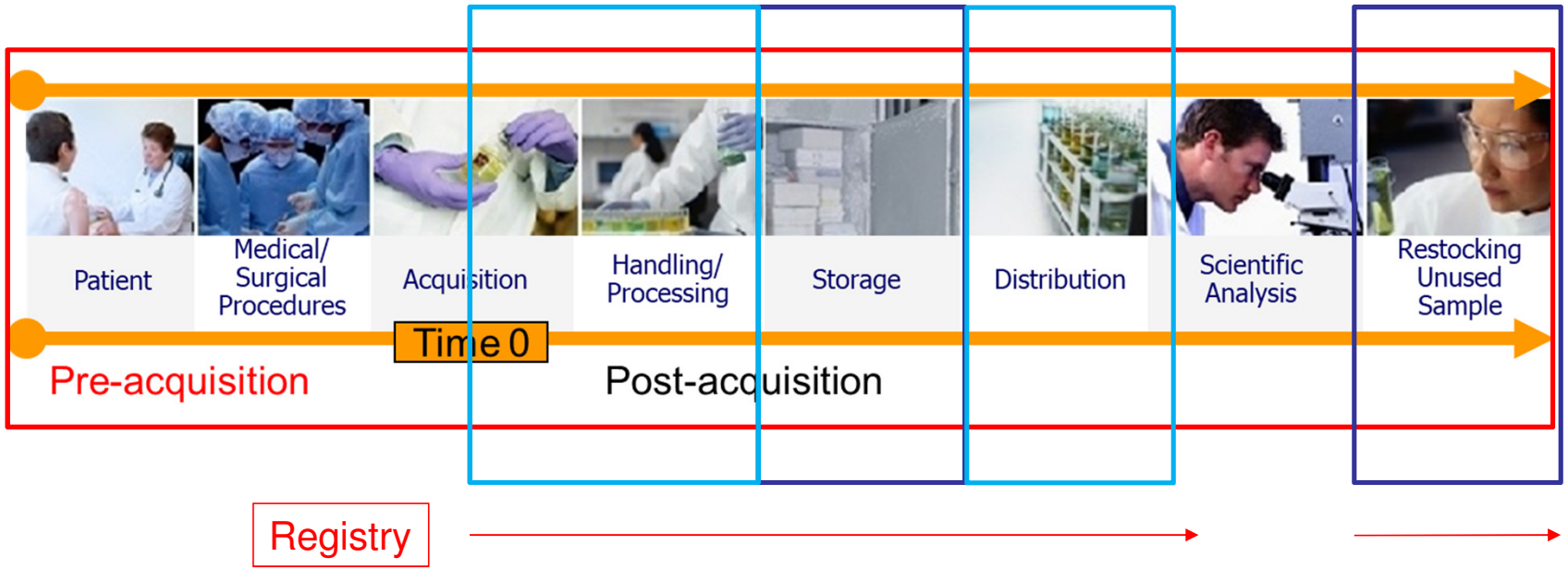


- Sharing and distribution of specimens

- Integrated in BB study approval flow
  - PU (~PI) <> SU (~CP)
  - Independent third party requests
    - Referred to interested parties within UZ/KU Leuven
    - Setup of collaboration
    - If agreement settled > submitted by (local) PI to biobank for approval

- Evaluation based on
  - Availability of the HBM (requested “amount” versus available in case of destructive testing) (consultation of the diagnostic departments for diagnostic HBM); Availability of required clinical data; Scientific soundness of the research proposal; Track record of the research group on the topic; Originality of research; Translational impact; Appropriate valorization; Cooperation from all involved parties; …

7. Handling of HBM as today



Phase 1 < OCT 2020

Phase 2 > OCT 2020

Phase 3 TBD

Return of results

- Moral consensus to return research results to participants
  - No universal/common policy/approach

- Legal obligation to return “significant information”
  - Clinically relevant and validated information available
  - Donor’s right to be informed (also to revoke ~ICF) <> anonymization
  - According to law regarding patients’ rights
  - PI should transmit information to BB manager
  - BB manager obtains donor’s identy through physician responsible for collection
  - BB manager will convey information to donor (assisted by relevant clinical profession)

Biobank priorities

- Align processes with GDPR implementation
- Single application form
- Align processes/templates (ICF, protocol,...) with CTC and EC
- COMMUNICATION: Website, trainings, ...
- Cell line dataset (& “live” storage)
- Connection with services/data diagnostical platform UZL

- Help you out!

Approach new studies & regularisation old studies

	Newly starting	Active sampling & use	Active use (sampling stopped)	Historical collection	Import/Export
CTC (S-nbr)	Y	Y	Y	Y (eg MLxxxx)	Y
BB approval	Y	Y = OK (amendments?) N -> obtain BB approval	Y = OK (amendments?) N -> obtain BB approval	Use > 1NOV2018 -> obtain BB approval No use > 1NOV 2018 ("idling") -> low priority*	Y = OK N -> obtain BB approval
EC approval	Y	Amendment if Δ ICF/study protocol	Amendment if waiver needed	Y or Amendment (waiver)	N if EC approval present (eg ext project) Y if EC absent
Registry	Y	• Collected/stored > 1NOV2018 • Used > 1NOV2018*	• Collected/stored > 1NOV2018 • Used > 1NOV2018*	Complete collection vs samples used*	Y

*view FAHMP: storage of historical samples = intention of (future) use – biobank law applies (BB approvement, registry)

=> Current priority for new and active studies, but historical collections should also be regularized and comply to the UZ KU Leuven Biobank framework

Overview HBM diversity

	Setup collection Primary Use (umbrella)	Setup collection Residuary Material (umbrella)	Primary Use (PU)	Secondary Use (SU) on HBM remaining after PU	Secondary Use (SU) on Residuary Material (RM)	Cell lines from PU (own production)	Cell lines - commercial (import)	Import – analysis or setup of collection	Export	CT[$]	CT[$] (optionally additional material for future use)
CTC	+	+	+	+	+	+	+ (light) (check mark application form CTC)	+ (light) (check mark application form CTC)	+	+	+
BBB	NE	NE BBB ZP	NE	NE BBB * ZP * * unless approved in umbrella	NE BBB * ZP * * unless approved in umbrella	NE	NE	NE	Cfr PU/SU, not necessary if already included in BB/EC approved protocol	notification	cfr PU (for optionally additional material)
duration	14d	14d	14d	14d	14d	14d	14d	14d	14d	NA	14d
registry	+ v1	+ v1	+ v1	+ v1	+ v1	+ v2	+ v2	+	+	-	-
ICF	+	- (check opposition at reception/distribution; by PI)	+	- if ICF PU covers research subject + or waiver if ICF does not cover (-> EC)	- (check opposition at reception/distribution; by PI)	+	- * ATCC -> eth. declaration * other -> to be provided by PI (or equivalent)	+ template (or equivalent) to be provided by PI	Category dep: PU + SU RM: -, protest SU OV: + if ICF does not cover SU OV: - if ICF covers	+	+
EC	+	+	+	+ if research subject is not covered by ICF	+	+	+ (light)	- If only analysis & external EC+ elsewhere + If only analysis and no ERB+ elsewhere	Cfr PU/SU, not necessary if already included in BB/EC approved protocol	+	+

[$] Klinische proef cfr compendium: klinische proeven met geneesmiddelen of proeven waar geneesmiddelen worden vergeleken met medische hulpmiddelen, zoals goedgekeurd door FAGG (opt HBM)
[$] clinical trial: clinical trials with medicines or trials in which medicines are compared to medical devices, as approved by FAMHP and EC

Common issues

- Umbrella protocols (systematic collections; commercial cell lines)
  - Collection protocols to systematically collect samples for a (group of) disease(s) and/or the use thereoff
  - Allowed (EC approval)
  - Study protocol:
    - Description of origin, quantities, intended use, storage period, destination/fate after use
    - If relevant: incorporate older studies* in the umbrella to update and align
    - If relevant: indicate which studies are currently making use of these samples
  - ICF:
    - clauses to allow future use (if approved by EC), commercial use
  - Actual use of samples in specific projects: project requires CTC/BB/EC approval
    - BB & exp law: donor has to give specific informed consent

* BB approval requires study protocols & ICF of older studies for oversight and traceability

Common issues

- Samples collected elsewhere
  - Within Belgium
    - If obtained from notified non-UZ KUL biobank & for analysis only & destruction/return of remaining material (incl derivs)

    ➢ No action required (comply to agreement with notified biobank)

    - If obtained from notified non-UZ KUL biobank & for analysis & storage of remaining material (incl derivs) for future use (and if allowed by protocol/consent)

    ➢ Study admission: CTC (S-number)/BB[$](/EC*); registry, storage @ biobank facility

    [$]provide study protocol, ICF template, MTA originating biobank

    *might be covered by third party EC approval: provide copy of EC approval to biobank

    - If obtained from non-notified non-UZ KUL biobank = ILLEGAL (1k-10k€, 1y-5y prison)

Common issues

- Samples collected elsewhere
  - Outside of Belgium (= import)
    - For analysis only and/or storage of (remaining) material (incl derivs) for future use (and if allowed by protocol/consent)
    - ➢ Study admission: CTC (S-number)/BB[$](/EC*); registry, storage @ biobank facility

      [$]provide study protocol, ICF template, MTA originating biobank

      [$]proof that samples have been taken according to local legislation and according to international ethical/privacy/personal data standards (eg. cell lines)

      *might be covered by third party EC approval: provide copy of EC approval to biobank

    - If obtained and used without registration in notified biobank = ILLEGAL

      (1k-10k€, 1y-5y prison)

Common issues

- Use of “left-over” (REMAINING!) material: additional EC/BB approval necessary?
  - Biobank law: secondary use requires (re)consent from donor
  - Completely dependent on original collection protocol, ICF and type of material and intention/scope of use
  - Donor’s consent! If Y/N clause for future use in ICF: check individual donor’s response!
  - “left-over” use in scope of original collection protocol:
    - No additional EC approval necessary
    - If deviation from BB approval (eg destination, ...) -> BB approval
  - “left-over” use NOT in scope of original collection protocol:
    - Additional BB and EC approval necessary
    - May require consent waiver from EC
  - Residuary material (≠ remaining): always requires EC/BB approval

Common issues

- What about derivatives?
  - **Law:** Human bodily material (HBM): any biological material, including human tissues and cells, gametes, embryos, fetuses, **as well as the substances derived therefrom**, whatever their degree of processing/transformation (DNA, RNA, proteins, …) (including – commercial – cell lines!)
  - **Compendium:** If human body material is stored for future research for which there is no agreement with a biobank, then this action triggers the obligations to notify oneself as a biobank
  - ➢ Should be incorporated in study protocol & biobank application
  - ➢ Registry: pragmatic approach, dependent on fate of derivative, and moment of creation
    - ➢ Consumed/destroyed at end of project (created after storage of parent <> storage of deriv until analysis) vs
    - ➢ Future use is considered > within intent of biobank law and UZ KU Leuven biobank policy applies (BB approval, registry, storage)

Common issues

- HBM not subject to the law
  - Eg control DNA in kits
  - Eg human serum as basis for cell culture
  - Eg routine validation of a device*
  - Eg academic (non-profit) training
  - ...

  ➢ The provisions on biobanks in the law only apply to scientific research (for the development of knowledge specific to the practice of healthcare professions) with human body material.

*If this would concern a new test or diagnostic procedure, the legislation applies.

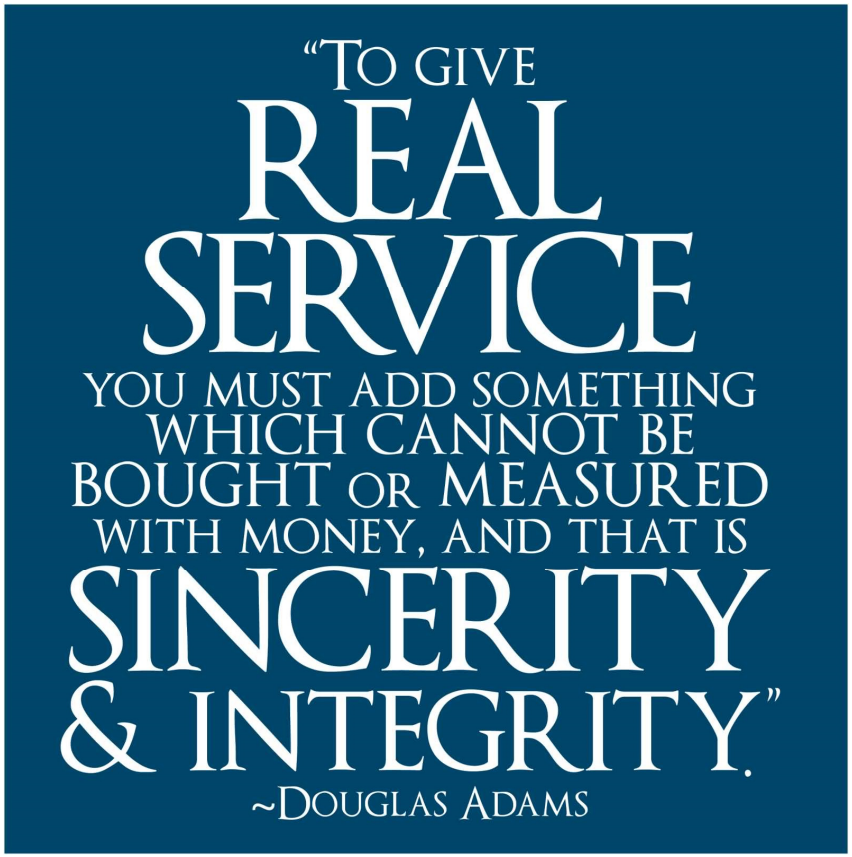
What to do next?

- Contact the biobank in order to:
  - obtain Biobank Board approval for your scientific study/project
  - register your samples in the Biobank Registry
  - centralize your HBM collections

Contact

- UZ KU Leuven biobank (= wetenschappelijke biobank) - wbb@uzleuven.be
  - Loes Linsen – Loes.Linsen@uzleuven.be – Dect: 016 344941
  - Mathias De Haes/Jessica Ratajczak - Dect: 016 346193
  - Nadine Ectors – Nadine.Ectors@uzleuven.be – Tel 016 34 54 85 (secr.)

Questions?


"To give
REAL
SERVICE
you must add something
which cannot be
bought or measured
with money, and that is
SINCERITY
& INTEGRITY."
~Douglas Adams