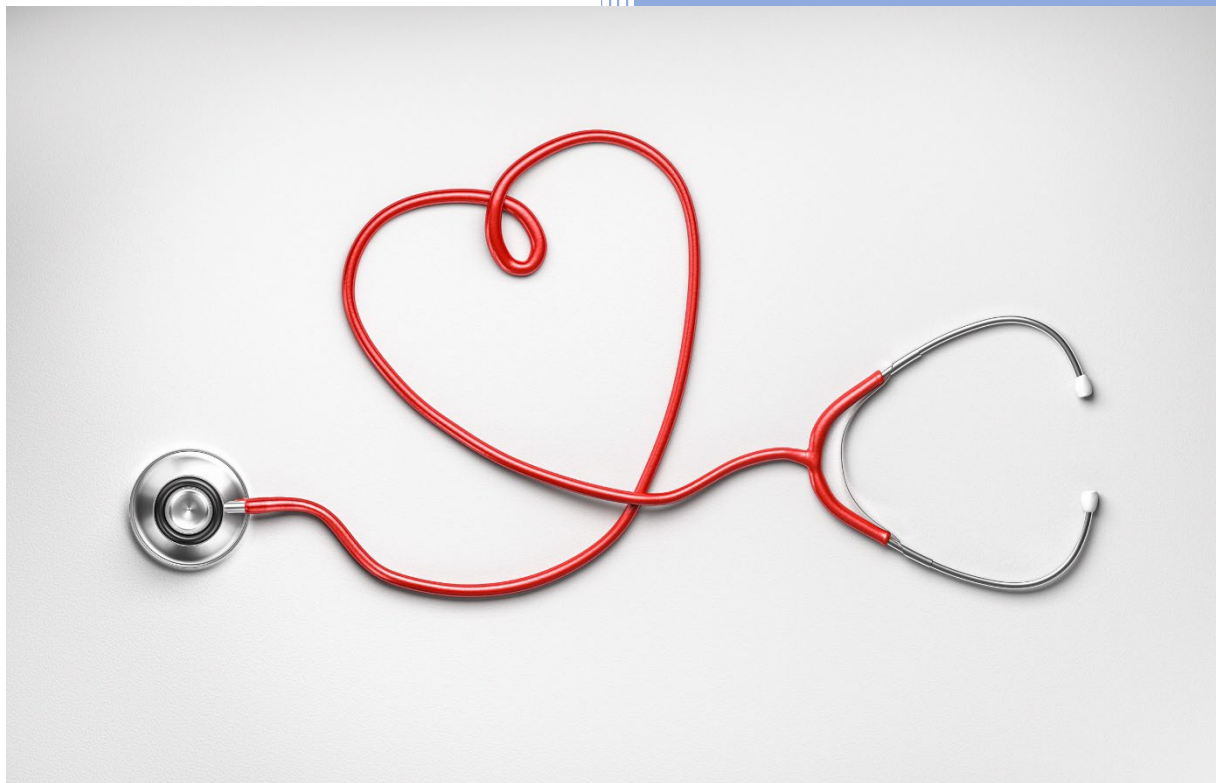


A national Heart Tissue bank: from 0 to 100 in 1 year?



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Index

Index 1

Introduction..... 2

Stakeholder analysis..... 3

Questionnaires stakeholders’ perception 4

Bottlenecks and possible routes to solution 6

Conclusion advice 9

Acknowledgements 9

Annex 1 Questionnaire 10

Annex 2 List of Dutch Biobanks 13

Introduction

Scientists from the Netherlands Heart institute, including Prof. Dr. Pieter Doevendans, and the chair of the Dutch patient organization Pieter Glijnis, initiated a new biobank in the Netherlands to collect heart tissue for research: The heart tissue bank or “Hartenbank”. The initiative first originated from research into the detrimental effect of PLN mutations on heart failure, yet aims to include tissue from healthy and diseased hearts.

The foundation is part of the Netherlands heart institute (NHI), a partner of the Dutch Cardiovascular alliance (DCVA) and received support and funding from the Durrer centre and Dutch Heart foundation, respectively. Currently, 10 employees are employed full-time or part-time. A scientific board is installed, including 5 Dutch scientists from several Dutch University medical centres.

Dutch-speaking donors can register through the website (hartenbank.nl). After the donor has passed away, logistics follow similar procedures as used for the national Brain tissue bank. The body is transported to the Expertise Centre for Post-mortem Diagnostics at Amsterdam UMC for autopsy according to established protocols. Following autopsy, the body is returned to the deceased’s family and the heart tissue is processed and stored along with the medical records (Figure 1). Scientists can submit a request to use tissues and data, which is assessed by the Data access committee, consisting of members of the scientific advisory board and the ethics committee of Amsterdam UMC.

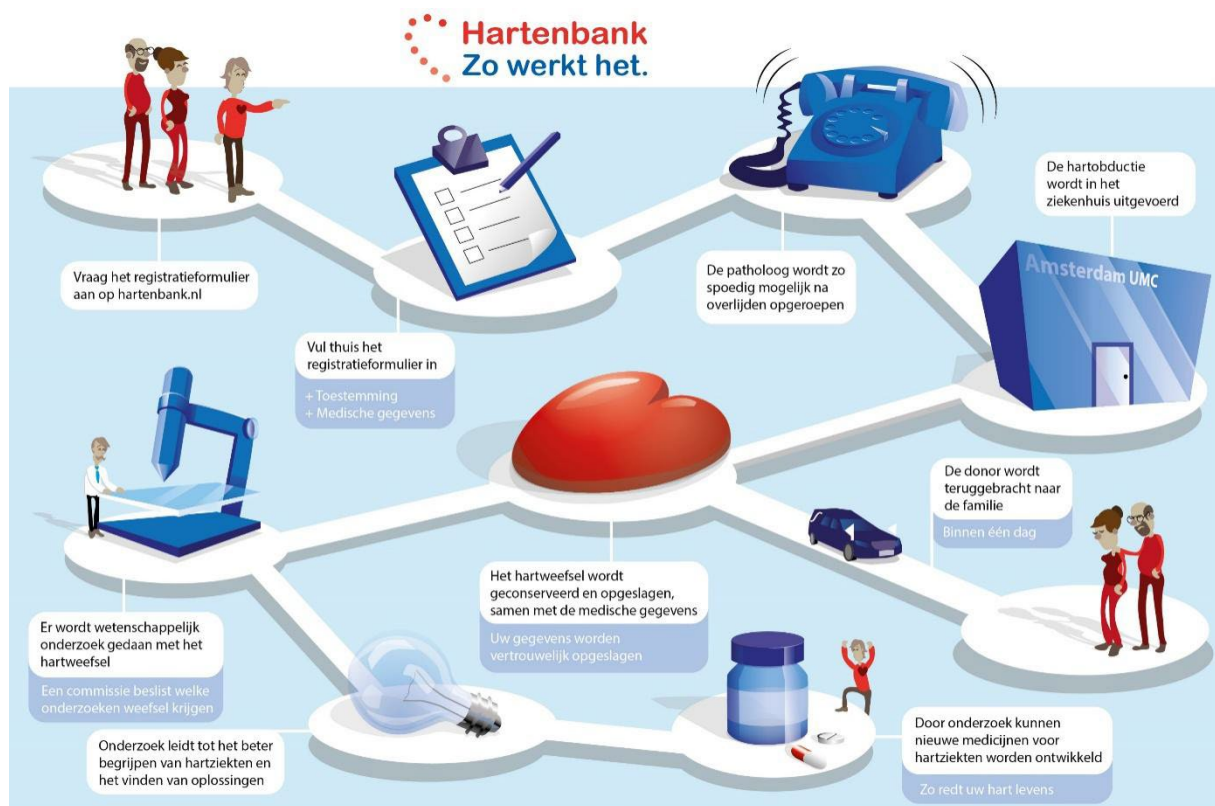


Figure 1. Procedure and logistics inclusion heart tissue in Heart Tissue Bank

Since the start, donor registration is increasing, however, inclusion of actual tissue was non-existent initially. Being part of the DCVA, the opportunity was taken to draw up an assignment for the members of the DCVA talent program to improve this aspect of the Heart tissue bank. Thus, the main goal of the assignment was to increase the inclusion of tissue samples into the bank. To achieve this goal, several interviews were conducted with the Heart tissue bank leadership to define stakeholders, obstacles and opportunities, and a stakeholder analysis was created. Further interviews and brainstorming with stakeholders, and among the assigned members of the DCVA talent program provided several viable or less viable routes, which will be discussed in this written report.

Stakeholder analysis

The Heart tissue bank is part of the NHI and funded by the Dutch Heart foundation. The national transplant foundation, donors (healthy donors and patients with heart disease), patient organizations, medical doctors (cardiologists, cardio-thoracic surgeons, pathologists), scientists and the national donor registry were identified as stakeholders. Both patients with heart disease and healthy subjects may donate heart tissue post-mortem. Patient organizations could have significant impact by informing their members and recruiting new donors with heart disease. Cardiologists, cardio-thoracic surgeons, and pathologists in the different University medical centres are or could be involved in logistics, and recruitment of new donors in a clinical setting or through the deceased's family. This can pertain both subjects with healthy hearts – not used for transplantation- as well as with heart disease. Their willingness and/or (in)possibilities to include subjects and deliver tissue, and thus their impact on the tissue availability in the Heart Tissue Bank needs to be clarified. The national donor registry might be a potential player to provide new donor hearts, a possibility which should be clarified further. The role of already existing biobanks in the Netherlands is also unclear and may have a positive or negative effect on the tissue availability in the Heart Tissue Bank depending on willingness to collaborate. Scientists are the end-users of the heart tissue, yet awareness and willingness to use tissue was unclear initially.

The Dutch and European Transplant Foundations, representing transplant patients and the families of donors, are unaware of the Heart Tissue Bank initiative. Moreover, the opinion of Dutch citizens on the topic 'Heart Tissue Bank' remains to be elucidated, yet these opinions are pivotal in generating a foundation for the Heart Tissue Bank. While being represented in the Heart Tissue Bank, the Dutch Heart Foundation can raise awareness among the Dutch population. The Dutch Heart Foundation already emphasizes on educating lay-men and experts in the Netherlands, thereby raising awareness of the Hartenbank would perfectly fit their strategy.

Additional analysis can still be performed if requested.

This stakeholder analysis and discussion with leadership of the heart tissue bank called for further clarifications of the stakeholders.

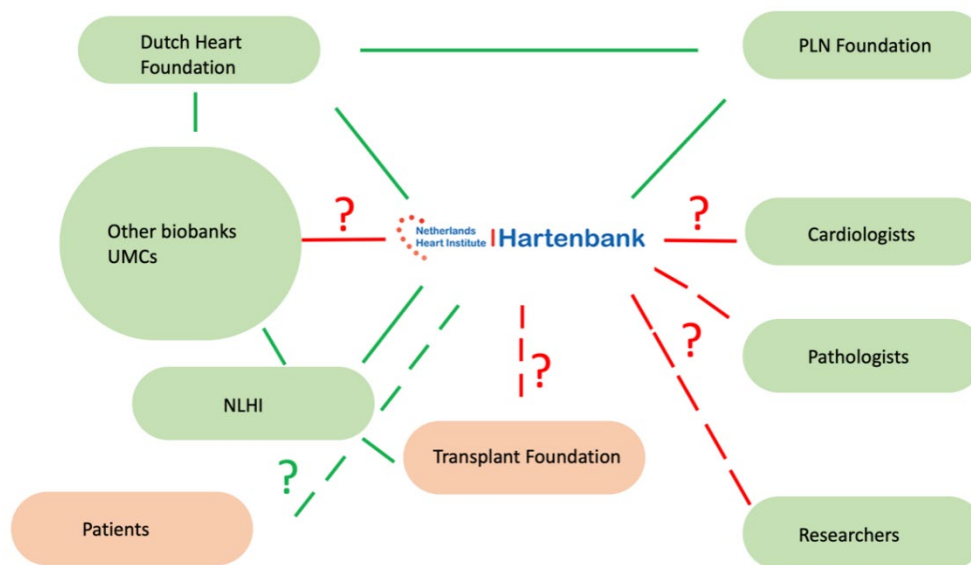


Figure 2. Stakeholder analysis.

Stakeholders in green have been analyzed in detail, stakeholders in red have not. Green lines indicate a perceived, positive connection, while red lines are uncertain. Uninterrupted lines are known connection, while dotted ones are not clear.

Questionnaire stakeholders' perception

A total of 22 clinicians and scientists at all University hospitals responded after being approached via interviews and/or an online questionnaire (appendix 1) to evaluate three main questions:

- What is the level of awareness among these stakeholders?
- What level of collaboration is present among the stakeholders?
- What other initiatives on heart biobanking are already available?
- What are opportunities and/or obstacles to collaborate with the Heart Tissue bank?

Over 60% of the respondents were already aware of the initiative, with clinicians being least aware (Figure 3). The initiative was deemed valuable (32%) or valuable in case of concrete goal (36%) by the majority. Two respondents did not consider the initiative to be valuable. One is of opinion that the Heart Tissue bank will meet difficulties in data sharing and usage of the tissue for research. The other one has no experience with this and find it hard to imagine the value of the Heart Tissue bank. Although nearly all respondents were willing to collaborate, the willingness to actively participate with tissue collection was only 60% (Figure 3). Both scientists and clinicians were represented among those not willing to participate. In addition, active participation was conditional to several concerns related to storage, financial compensation for supporting staff, impact on time, complicated organization, lack of/complicated infrastructure, as well as perceived issues with ethical approval and governance. This was reflected in the personal interviews with transplant centres and pathologists, who expressed similar concerns.

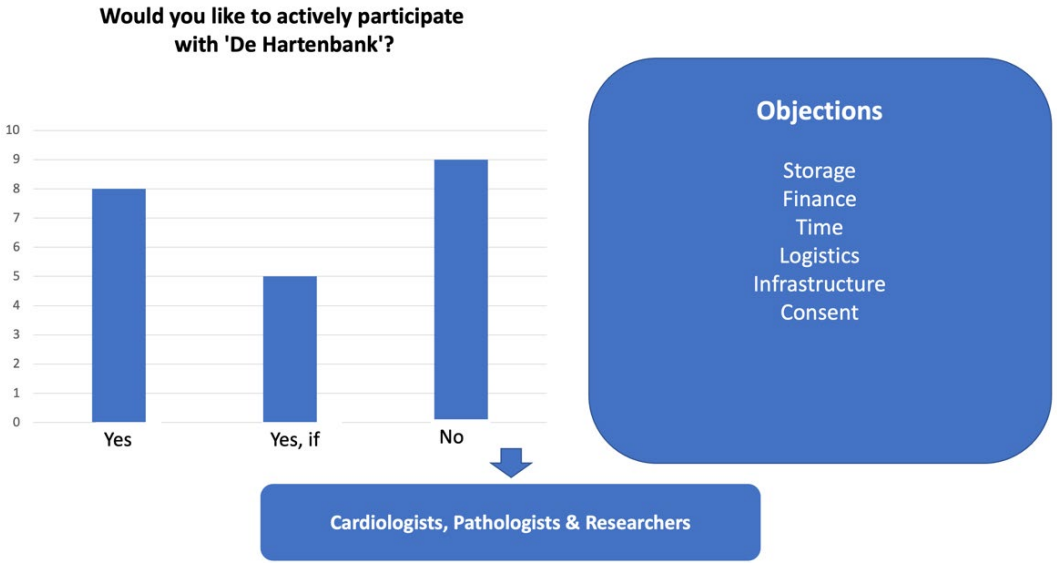
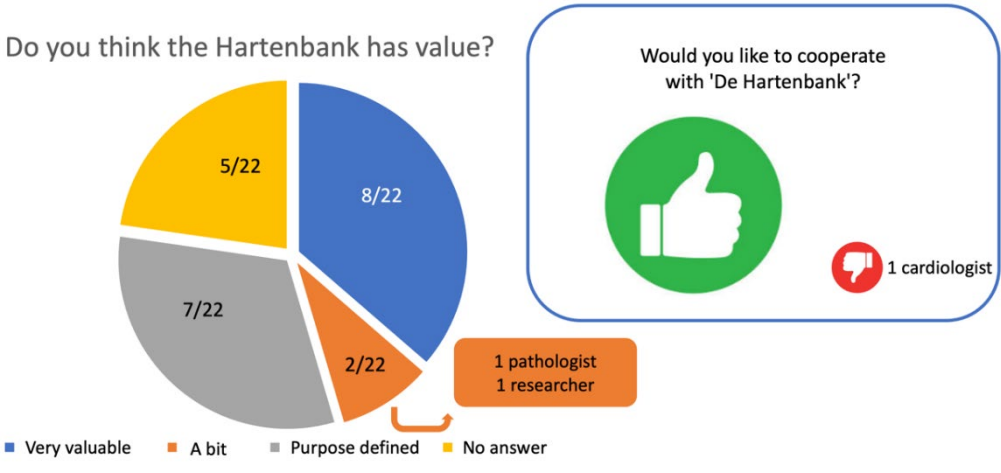
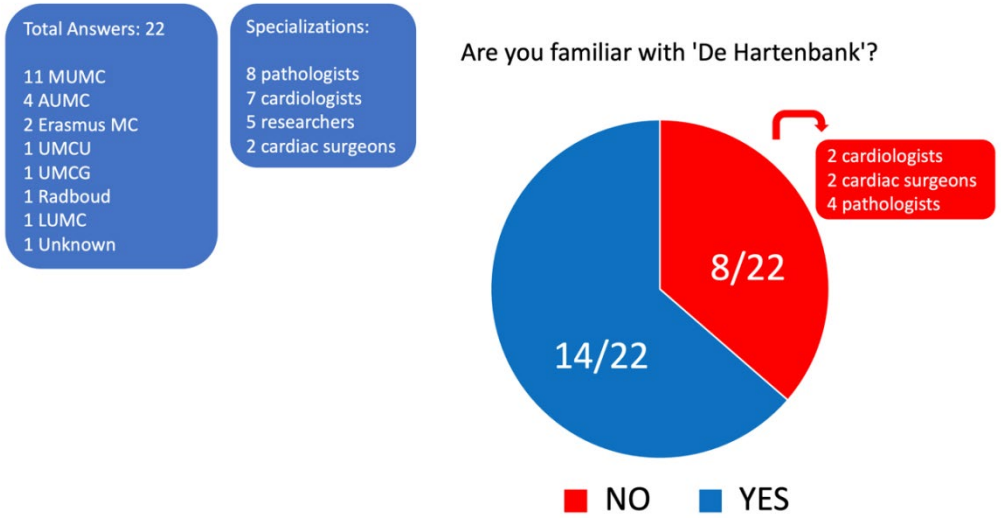


Figure 3. Results of the questionnaires

Bottlenecks and possible routes to solution

The overall goal of the assignment was to increase tissue availability in the biobank. Interviews, questionnaires, and discussions with the assigning party and the assigned gave the following insights.

1. Expanding supply

Tissues supply expansion may be achieved via various routes, including awareness among all stakeholder groups using social and traditional media, and fundraising activities. Indeed, the Heart tissue bank has initiated several public relations initiatives, including social media posts, an article in national newspaper “De Volkskrant”, and participation in the Dutch heart foundation’s charity event “Cycle Paris”. In addition, a video to raise awareness is being developed for social media posting.

Prospective recruitment via a centralized biobank may consist of expanding the donor populations beyond the current patients with laminopathies and PLN mutations to include healthy donors or other heart disease patient populations. To make use of existing infrastructures of patient associations such as the PLN Foundation and LMNAcardiac would be a very judicious and accessible approach. Recruitment of donors among living subjects could be achieved by coordination at national level via the national donor registry and/or with the Dutch transplant centres for both explanted diseased hearts, as well as non-usable transplant hearts. A national biobank would have obvious benefits in content size, international visibility, and financial efficacy. Additional recruitment of donor tissue of deceased subjects may be achieved via autopsy following approval by the deceased’s family. A complication here is the reportedly low approval by family members. A national communication campaign on the importance of autopsy-derived material for medical advancement is reported as a solution. The aforementioned video could also be used for this purpose.

Another increase in heart tissue may arise upon retrospective inclusion following connection with already existing heart tissue biobanks. This was mainly considered as a virtual connection, rather than a physical transfer of stored tissues to one central location. Thus, retrospective inclusion, would in effect result in a decentralized biobank. Although a big opportunity, several obstacles are identified, which will be discussed below. A list of existing biobanks is provided in annex 2.

2. Financial support infrastructure

Most stakeholders interested in retrospective or prospective collection expressed the need for financial support to hire staff to manage tissue collection, and retrieval, storage infrastructure and IT solutions. Thus, funding must be sought to overcome this obstacle. National opportunities should be explored to this end. The business case, financial support and overall finances are still unclear. Further exploration should be performed. Our advice is to inform how the Brain Tissue Bank works and other options could be to have a collaboration

with BBMRI-NL2.0 or to apply for `NWO Nationale Roadmap Grootschalige onderzoeksfaciliteiten`. First however, the required budget should be further estimated in current scale and after potential up-scaling to implement this infrastructure in the Netherlands in a durable way.

3. Logistics

A threat to success and comparability of tissue would be the failure to align protocols, as each institute has their own procedures. This was already recognized by the Hart tissue bank, and hence there is a one autopsy centre operating with one protocol. However, other centres considering to cooperate would need to agree on this location and procedure. A disadvantage of the current centre is its location in North-Holland, not the preferred central location as indicated in the interviews. One central person or team for coordination would be advisable. However, 3 locations through the Netherlands could also be an option to broaden the inclusions.

For inclusion of retrospectively collected tissue, it is likely there are inherent differences in procedures, collected anatomical sites, and databases used, amongst others, arising from multiple, decentralized locations. This would jeopardize comparability and superior quality data and should be characterized in detail before a decision on a merger is made. Moreover, for a virtual merger, connections between different software database systems and potential prohibitory rules related to hospital policy must be explored.

4. Potentially conflicting interests and governance

The transplantation centres in the Netherlands have already set-up a heart tissue biobank, to a varying extent. Currently, there is no great perceived benefit for the centres. Instead, issues with ownership of tissue, data and subsequent recognition on scientific articles are considered and threaten the incentive to collaborate. Clear agreements on these aspects might be pursued to overcome perceived resistance. Also, an inclusive governance structure for approval of tissue reuse was suggested. Thus, the existing scientific advisory board may be expanded with representatives of existing biobanks.

5. Ethics

Local ethical approval for donor inclusion and tissue collection has been granted by the Medical Ethics committee of AMC. Reuse will be reviewed by the scientific advisory committee of the Heart Tissue Bank and by the AMC's "Biobank Toetsings Commissie". Yet, several concerns have been expressed. For both retrospectively and prospectively collected tissue, clarification with local medical ethics committees is warranted to ensure ethics of tissue

collection and distribution. This should also pertain potential post-mortem inclusion following approval of the deceased’s family. As a new autopsy law “wet op de lijkbezorging” is pending, thus consultations with pathologists and ethics are necessary.

Analysis

We emphasize the need to distinguish retrospective versus prospective, and central versus decentralized approaches for Heart Tissue bank governance (Figure 4). Key questions arise in the discussion how to compare existing datasets. In retrospective studies, the quality of the tissues, timing and storage techniques might differ, which make them poorly comparable. To make the data equivalent in the future, the Heart Tissue bank can initiate uniformity in terms of protocols, collection and storage methods, informed consent and costs incurred.

All future routes to follow have their own specific pros and cons to consider. Whereas the Heart Tissue bank might benefit from one central section / obduction location in terms of clarity in communication and protocols, the willingness of potential donors may decrease due to longer absence of the donor for their loved ones. This might also lead to less willingness to be registered as a Heart Tissue bank donor, leading to a decrease in the rate of expansion of the Heart Tissue bank. A nearby University Medial Centre in a decentralized approach may lead to an increase in personal contact between potential donor and their physician. On the other hand, more locations will increase the expenses which need to be covered as well. Furthermore, all University Medical Centers have their own established protocols, and effort will be needed to find a consensus in one Heart Tissue bank protocol. Willingness of cardio-pathologists and other stakeholders is pivotal in an agreement to ensure one dedicated Heart Tissue bank protocol for section and storage.

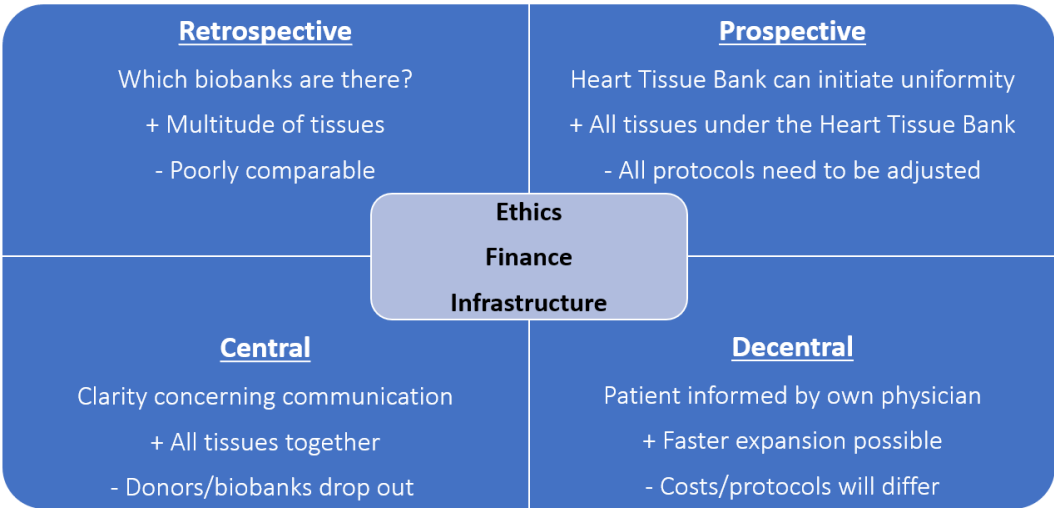


Figure 4. Retrospective vs prospective and central vs decentralized approaches for Heart Tissue bank governance

Conclusion advice

Since the start of the assignment the first heart has been collected and stored in the Heart tissue bank. To accelerate this further, several options exist and have been discussed. In general, our advice is to:

- 1) Investigate additional sources of funding to overcome a large obstacle and serve as a financial incentive for stakeholders. Preferably an application would include at least one of the transplant centres,
- 2) Contact the national donor registry to investigate potential connection,
- 3) Discuss ethics with local medical ethics committees and apply for appropriate ethical approval,
- 4) Organize a round-table discussion with stakeholders of the transplant centres to specify regulations and ethics around re-use of both retro- and prospectively collected tissue, and clarify other incentives to collaborate beyond financial issues,
- 5) Maintain and extend PR to increase awareness of the Heart tissue bank and generally use of bio banked tissue, possibly by hiring a PR/communication advisor to draw up a full communication plan.

Since cardiovascular disease includes the vasculature, we propose to consider extension to healthy and pathologic vascular specimen upon take-off of heart tissue inclusion.

Acknowledgements

We extend our gratitude to the leadership of the heart tissue bank, and all interviewed stakeholders to share their opinion.

Appendix 1 Questionnaire

Vragenlijst Hartenbank

De Hartenbank een opdracht gegeven aan deelnemers van de DCVA talentopleiding om (on)mogelijkheden voor de Hartenbank in kaart te brengen. Daarom vragen wij uw medewerking om onderstaande vragen in te vullen. hartelijk dank voor uw hulp, dr. Kak Kee Yeung, dhr Rogier Veltrop, en prof. Judith Sluimer



1. **1. Wat is uw functie, en vakgebied /specialisatie?**

2. **2. Bent u bekend met de hartenbank?**

Markeer slechts één ovaal.

- Nee, zie dan hier voor meer informatie: <https://hartenbank.nl/> en vraag 4
- Ja, zie vraag 3

3. **3. Als u bekend bent met de hartenbank, hoe beoordeelt u de waarde van de hartenbank?**

4. 4. Zou u met de Hartenbank samen willen werken? Zo ja, in welk vorm?

5. 5. Zou u actief willen participeren aan de hartenbank, bijvoorbeeld door het uitnemen van hart en/of opslag van weefsels?

6. 6. Wat zou voor u een mogelijk bezwaar zijn om mee te werken aan de hartenbank? Denk bijvoorbeeld aan opslagcapaciteit, infrastructuur, politiek of (gebrek aan) financiële middelen

7. 7. Met welke biobank / hartbank / vaatbank bent u bekend in uw instituut?
Svp naam, website, contactpersoon, type weefsel, ziekte of gezond vermelden

8. **8. Doet u reeds onderzoek met materiaal uit een biobank?**

Vink alle toepasselijke opties aan.

Ja, zie vraag 9

Nee

9. **9. Wat voor soort onderzoek, bijvoorbeeld hart/vaatonderzoek, wie is de contactpersoon?**

Hartelijk voor uw medewerking!

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Appendix 2 List of Dutch Biobanks

Institute	Biobanks including cardiovascular tissue
MUMC	Biobank Maastricht, Central biobank MUMC, Biobank CTC-, Biochemistry aorta biobank, CTC-electrophysiology, Maastricht Pathology Tissue bank
AUMC	Durrer centre, Cris dos Remedios/ Sydney Heart Bank, Autopsy biobank infarct and myocarditis, Marfan, Aortabiobank (valves and heart tissues)
Erasmus	BIOMArCS, biobank pathology department
UMCU	UMC Utrecht Heart Failure Cardiac Tissue Biobank, AtheroExpress carotid arteries with atherosclerosis
UMCG	Biobank with skin biopsies and serum*
UMC	Radboud Biobank*
LUMC	Aortic valves, Cardiothoracic Surgery biobank (valves and heart tissue)

CTC, Cardiothoracic; *heart tissue collection not specified