Annual report 2019

Biobank Research Ethics Committee (TCBio) UMC Utrecht

UMC Utrecht

Contents

Preface

With this annual report, the Biobank Research Ethics Committee (Dutch: TCBio) reports its contribution to the biobank governance structure in the UMC Utrecht in 2019. The increase in the number of release protocols reviewed in 2019 can be seen as a positive trend indicating more independent review of patient's rights in human tissue research. This should enhance patient's acceptance of this type of research. At the same time it helps researchers carry out their research with respect for patient's rights. In the present system however, the committee acts as a proxy for the donors. More involvement of donors in the future may also add to the acceptance of the Biobank Review system. As an example, in the reported year the Wilhelmina Children's Hospital (Dutch: WKZ) children's advisory board provided input for the new model recontact letter.

The increase in the number of release protocols in the years since the biobank policy came into effect also means the capacity of the meetings have now reached their limit. At the same time, due to the monthly frequency of the committee meetings, the committee's response time cannot be reduced any further. In order to keep up with the increasing workload and to facilitate an efficient and rapid review system, steps will need to be taken to expand capacity further by increasing the meeting frequency.

Prof. J.J.M. van Delden (MD PhD, chair)

Summary

In 2019, the total workload of the committee increased again compared to previous years. This was mainly due to an increased number of requests for release of human biological material reviewed by the Biobank Research Ethics Committee (BREC, Dutch: TCBio) UMC Utrecht. In addition, the number of amendments increased again as well.

The committee aims to complete the review in as short a time as possible. The number of days needed to review the protocols decreased again slightly in 2019. With the present meeting frequency however, the committee's review time cannot be reduced further. In order to facilitate a rapid review process, an increase in meeting frequency appears the main solution as other measures, such as mandating the chair for non-substantial amendments, have been exhausted.

The number of unfinished procedures decreased compared to 2018 thereby reducing wasted committee time. However, analysis of the applicant's response time shows a substantial number of applicants take a long time, sometimes many months, to respond to questions adding to inefficiency of the review system. To increase review efficiency the divisions could be encouraged to analyze the reasons behind these long responses.

Chapter 1

Competent Authority BREC (Dutch: TCBio)

The Biobank Research Ethics Committee (Dutch: Toetsingscommissie Biobanken - TCBio) is an independent committee appointed by the UMC Utrecht board of directors as a result of the UMC Utrecht Biobank Regulations[1] adopted by the Board of Directors in 2013.

UMC Utrecht Biobanks, consisting of human biological material and associated data are increasingly important for medical scientific research. Typical for a biobank is that the specific research question for which the human tissue material will be used, is only globally known at the time donors make their material available to the biobank. Also, in most cases the investigator does not know for which specific purpose the material will be used and by whom. At the time of donation to the biobank, the donor actually gives away part of his control rights over the material to the biobank. To ensure support for biobanks now and in the future, donors have to be able to trust that their material and data will be handled in a proper manner in the biobank and during the medical scientific research.

The following aspects are important for the trust of donors:

1) protection of confidentiality of the material and the data,
2) manner of consent of the donor,
3) return of results,
4) ownership of the material,
5) commercial use.

The issues above have been worked out in the UMC Utrecht Biobank Regulations. With the Biobank Regulations the UMC Utrecht aims to build a high quality infrastructure for medical scientific research for all UMC Utrecht investigators and her partners. To reach this goal, the Biobank Research Ethics Committee reviews whether the human biological material and data are collected and stored in a responsible way in the UMC Utrecht biobank according to the criteria of the Biobank Regulations. Similarly, the committee reviews whether the material and associated data will be used in a responsible way in scientific research. This governance model doesn't solely serve the interests of the donors but also those of the researcher and society as a whole by making sure that the (scarce) material will be used for the right projects. Donors have to be able to trust that their material and data will only be used for relevant scientific research. In addition, the quality and registration of the human biological material in the biobank is guarded by the Central Biobank UMC Utrecht.

1 Link to UMC Utrecht Biobank Regulations: https://assets-eu-01.kc-usercontent.com/546dd520-97db-01b7-154d-79bb6d950a2d/ae4726d2-b6eb-407b-a576-db1a5c63a139/Biobank_Regulations_UMCUtrecht.pdf

Chapter 2

Committee members

New members are recruited through the divisions of the UMC Utrecht or proposed by members leaving the committee. In 2019 the main changes to the committee were: Dr. C. (Caroline) van Baal (epidemiologist) was replaced by epidemiologist dr. P.M.J. (Paco) Welsing, dr. W.(Wigard) P. Kloosterman (geneticist) was replaced by geneticist prof. dr. J.K.(Hans Kristian) Ploos van Amstel, prof. dr. T. (Tim) Leiner (radiologist) was replaced by radiologist dr. F. (Firdaus) A.A. Mohamed Hoesein (radiologist), privacy officer mr. S. (Susanne) Salomé-Kempjes was replaced by drs. D.A.H. (Dennie) Gullikers-Schoonderbeek (privacy officer). Finally, laywer dr. Mr. G.E.T. (Geranne) Lautenbach was replaced by lawyers mr. G. (Gaby) V. Minasian and mr. B. C. (Claire) Collins.

A complete list of the committee members as of January 2020 is given in attachment 1.

Chapter 3

Office employees

The office is part of the Department of Research Review (Dutch: Afdeling Toetsing Onderzoek) which supports two committees: the Medical Research Ethics Committee (MREC, Dutch METC) and the Biobank Research Ethics Committee (BREC: Dutch TCBio). Head of Department is Mrs. S. de Weerd. The office employs four secretaries, three review procedure coordinators and one person performing administrative duties. The Department is part of the Directorate Quality of Care & Patient Safety. A list of the office employees in 2019 can be found in attachment 1.

Chapter 4

Committee operating procedure

Committee meetings take place monthly, every 3rd Thursday of the month (12 times in 2019). In general, the operating procedure is comparable to that of an accredited MREC and has been described extensively in previous annual reports. The rules of procedure can be found on Connect pages of the committee: https://intranet.umcutrecht.nl/connect/onderzoek/biobank/Paginas/Other-information.aspx

4.1 Plans for 2020

A) In the past years, processes have been optimized to reduce the committee's review time. These optimizations included optimization of the templates to reduce the number of rounds of question's and mandating the chair to review non-substantial amendments (section 5.5). While the mean review time decreased again slightly in 2019 (section 5.4), it is still not within the review time set by the committee's rules of procedure. The monthly frequency of the committee meetings likely is the largest contributing factor in the longer review times.

   Therefore, to reduce the review time further, in 2020 preparations will take place to increase the frequency of the meetings to every other week by January 2021. These preparations include preparing a board of directors decision to increase capacity at the office to support the committee.

   During the year 2020, due to the exceptional circumstances of the COVID-19 crisis, the committee allowed a fast track review procedure for research that that needs to start immediately and for which the monthly frequency would seriously hamper the possibility to start the research on time. The researchers need to give arguments why a fast track procedure should be granted based on scientific and societal impact and will be allowed in exceptional circumstances only.

B) The information on the procedures and templates is available on the UMC Utrecht intranet Connect (see 5.9) and can therefore not be accessed by external partners. While the UMC Utrecht Biobank Regulations demand that the Biobank review procedures can only be submitted by UMC Utrecht employee's, there is sometimes a need to have information on the procedures and templates available to external collaborating partners.

   Therefore, in 2020 a new BREC (TCBio) website will be set up as part of the UMC Utrecht corporate website to make the information available to partners outside of the UMC Utrecht. At the same time the layout of the information will be updated.

Chapter 5

Review of sub-biobanks and release protocols

There are two types of protocols: sub-biobank protocol (Dutch: deelbiobankprotocol) and release protocols (Dutch: uitgifteprotocol).

5.1 Sub-biobank submissions

5.1.1 Total number of sub-biobank submissions to MREC (Dutch: METC) and BREC (Dutch: TCBio)

As for 2018, the total number of sub-biobank submissions increased again in 2019. This increase was largely due to an increased number of sub-biobanks being set up in combination with studies reviewed by the MREC[2] (Figure 1).

Sub-biobankprotocols submitted to METC and TCBio 2014-2019

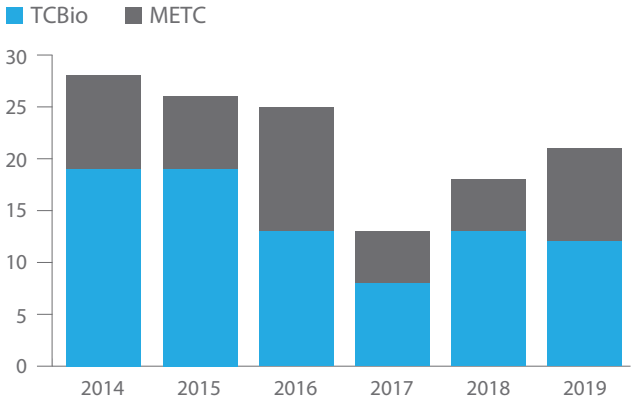

Figure 1. Number of sub-biobank protocols submitted in 2019 versus previous years

In addition, as the number of active biobanks increases so does the number of amendments to sub-biobanks, increasing the committee's workload. See 5.5

5.1.2 Outcome Sub-biobank reviews by BREC

In 2019 no sub-biobank submissions were rejected (Figure 2). In all cases where the review procedure was completed, the committee advised positively to the Board of Directors (BoD). One submission was referred to the MREC for re-evaluation of whether the proposed biobank was subject to the Medical Research involving Human Subjects Act (WMO). For three other submissions the review process was still ongoing at the time of writing.

Outcome TCBio review sub-biobank protocols 2013-2019

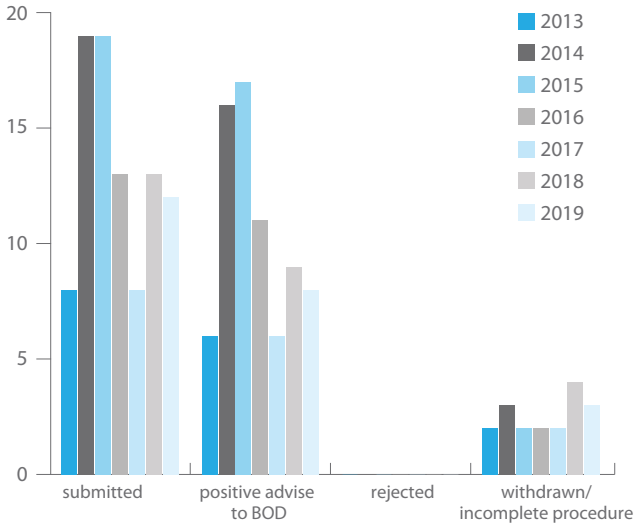

Figure 2. The outcome of sub-biobank review procedures by BREC in 2019 compared to previous years (2013-2018).

2 As requested by BREC, the MREC reviews sub-biobank protocols when human tissue for the biobank is collected from the same research subjects that take part in a research protocol for which review by the MREC is compulsory (WMO review). Thus, the two review procedures are combined and the applicant only deals with one committee.

5.1.3 Sub-biobank submissions represented by UMC Utrecht Divisions

The number of sub-biobank submissions varies across the UMC Utrecht divisions (Figure 3). Due to the small numbers, no trend is visible.

BREC submissions 2019 by UMC Utrecht division - sub-biobanks

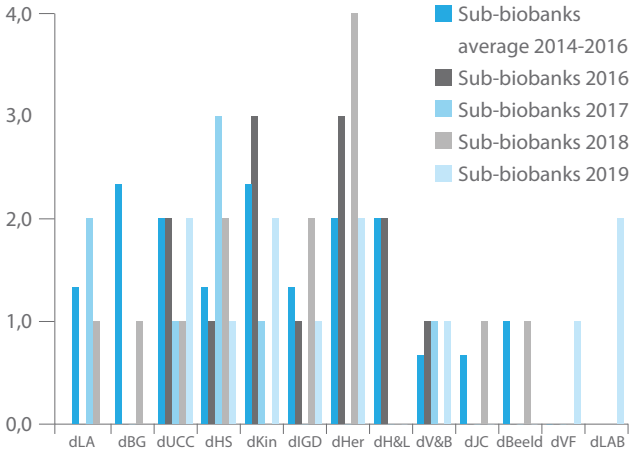

Figure 3. Sub-biobanks submissions by division in 2019 compared to 2018, 2017 and 2016 and to the average number of submissions in 2014-2016.

Note: Due to the merger between divisions dBG and dLA into the new division dLAB there is no separate data for the former two for 2019.

5.2 Release protocols

5.2.1 Release protocols submitted for review

The number of release protocols submitted continued to increase in 2019. With a meeting frequency and duration of once a month and 2.5 hours respectively, each meeting schedule is filled to capacity.

Release protocols submitted 2012 - 2019

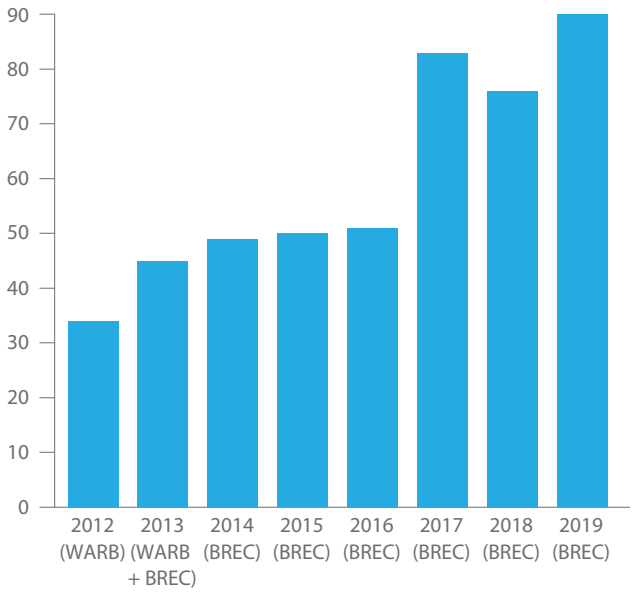

Figure 4. Number of release protocols submitted for review represented by year.

In addition, as the number of active release protocols increases so does the number of amendments to these, increasing the committees workload. See section 5.5.

5.2.2 Outcome release protocol reviews

In 2019, the number of release protocols submitted increased again (Figure 5). Around 75% of the submissions were completed in 2019 and a further 14% are expected to be completed in 2020.

Of the completed review procedures, two release protocols were rejected. In both cases, the committee concluded that the intended use of the human tissue material did not fall within the broad consent given by the donors (Article 10a sub (6) UMC Utrecht Biobank Regulations) and rejected the proposal.

The committee's agenda is generally filled to capacity. As seen in figure 5, in the last few years a substantial number of reviews are not completed (23 % of the total in 2019) even after the first quarter of the following year. While the committee aims to complete the review as fast as possible, figures show that the time the applicant takes to return answers to committee's questions is in many cases substantially longer compared to the committee's time. This will be discussed in more detail below (section 5.4.1).

Fewer submissions were withdrawn during the review process compared to 2018 (1 vs 3). One submission was referred to the MREC for WMO-review. Five submissions (5,5 % of the total compared to 12% in 2018) have not been completed for unknown reasons despite reminders. In principle, applicants are given two months to respond to committee's questions. Applicants are informed that without a resubmission within 2 months, the file may be closed. When necessary, applicants can ask for an extension.

As of the end of 2018, the office has put in place a system to more actively keep track of non-responders and issue timely reminders. When applicants still fail to respond, they are informed that the review process is terminated. The applicant's division receives a copy of the termination. This seems to have had a positive effect as the percentage of incomplete procedures decreased in 2019.

Outcome TCBio review release protocols 2019

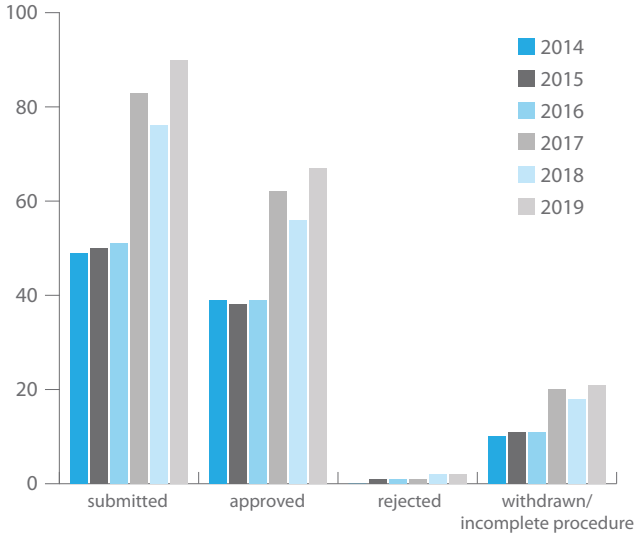

Figure 5. Review outcome release protocols in 2019 compared to previous years as of end of April 2020.

5.2.3 Release protocol submissions represented by UMC Utrecht Divisions

The UMC Utrecht divisions dLA and dBG submitted the highest number of release protocols.

BREC submissions 2019 by UMC Utrecht division - Release protocols

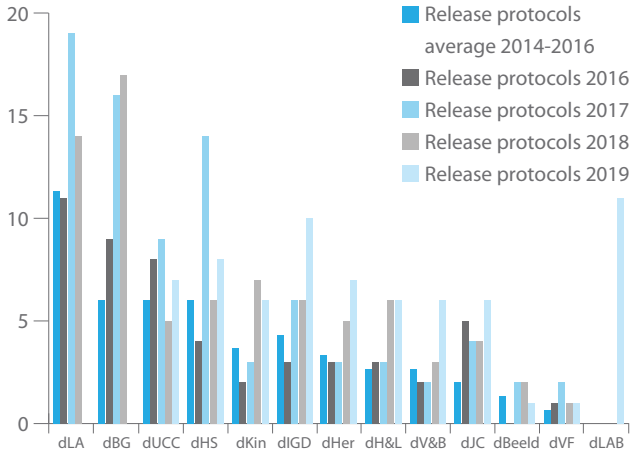

Figure 6. Release protocol submissions by UMC Utrecht division in 2019 compared to the average number of submissions in 2014-2016 and the number of submissions in 2018, 2017 and 2016. Note: Due to the merger between divisions dBG and dLA into the new division dLAB there is no separate data for the former two for 2019.

5.3 Total number of sub-biobank and release protocols submitted

As an indication of the committee's workload, figure 7 shows the total number of new biobank and release protocols submitted. While the number of sub-biobank submissions remained at a similar level compared to 2018, with 90 submissions the number of release protocols increased again compared to both 2017 and 2018. This increase may indicate that more research is performed or an increased awareness of researchers of the UMC Utrecht biobanking rules. An increased awareness may be due to a more active research quality policy within the UMC Utrecht regarding research not subject to the WMO. The increased awareness is further illustrated by a more even spread of submissions over divisions (Figure 8). In addition, the number of amendments also increased substantially (see paragraph 5.5) further increasing the committee's workload.

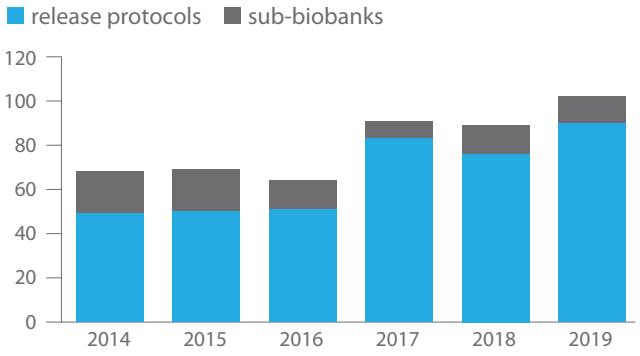

Figure 7. Number of sub-biobank and release protocols added together submitted in 2019 compared to previous years.

Total number of submissions in 2019 (sub-biobank and release protocols) by UMC Utrecht division

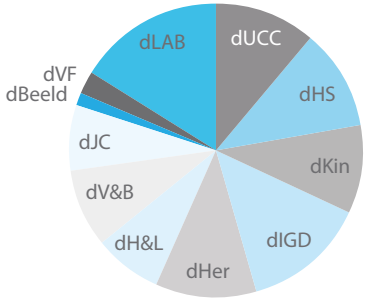

Figure 8. Number of sub-biobank and release protocols added together submitted per division in 2019.

5.4 Review procedure time-limits

The average time needed to complete the review procedures in 2019 decreased again compared to previous years (Figure 9). For release protocols, the review time still exceeds the time allowed in the committee's Rules of procedure (Dutch: Huishoudelijk reglement) document. The duration of the committee meetings was increased in steps from 1.5 hours in 2013 to 2.5 hours in 2016. With the present number of submissions, the meetings are filled to capacity.
At present, the committee meetings are held once a month. To substantially decrease the review time further, the meeting frequency would need to increase e.g. to twice a month.

Duration of review procedure 2014 -2019

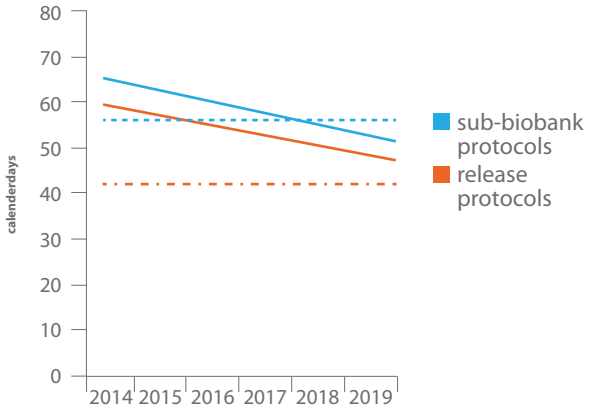

Figure 9. Trendline of average number of days needed for the committee to complete the review process for protocols submitted in the years reported. Data for release protocols in 2019 shows reviews completed by the end of May 2020 (n = 75, mean review time 44,5 days).

Sub-biobank review time-limit: 8 weeks (56 days)- blue dotted line
Release protocol review time-limit: 6 weeks (42 days) – orange dotted line

5.4.1. Applicant and committee response times

The total duration of the review procedure also includes the applicant's response time. In this annual report these data are included for the first time. The grey bars in figures 10 and 11 show these response times for sub-biobanks and release protocols respectively. While for two third of the release procedures the applicant's response time is less than 60 days, the majority of the remaining release protocol procedures are much longer.

The applicant is given two months to reply to committee questions after which the application file will be closed if no response is received by that time. In practice however, more time is given to respond before an application file is closed. In addition, as of 2018 applicants receive reminders if they substantially exceed the time limit. While the number of unfinished procedures has been reduced in 2019 (section 5.2.2), the substantial number of long and potentially never completed procedures creates an inefficiency and waste in the, already stretched, review system. The reasons for the long response times by applicants/researchers are unclear.

Review time in days for biobank protocols (n=12) submitted in 2019

(review procedures per 22 May 2020, 2 still ongoing)

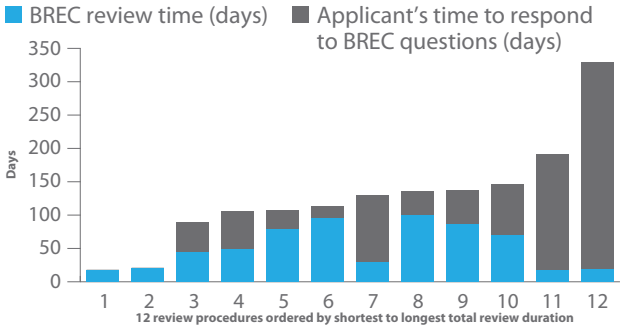

Figure 10. BREC review time and applicant's response time may consist of one or more rounds added together. Mean review time BREC: 51,8 days; mean total response time applicant: 75 days

Review time in days for release protocols (n=86) submitted in 2019

(review procedures per 22 May 2020)

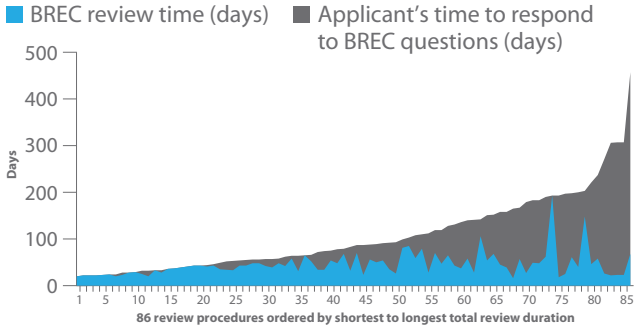

Figure 11. BREC review time and applicant's response time may consist of one or more rounds added together. The figure includes 11 review procedures for which no response was received by 22 May 2020. Mean review time BREC: 45,4 days; mean total response time applicant: 61,8 days

5.5 Amendments

In 2019, the number of sub-biobank and release protocols that were amended one or more times increased again substantially. Both the number of protocols that were amended and the amount of correspondence regarding the review of these amendments increased. As the total number of protocols that have been reviewed in the past increases, so does the potential for amendments to these protocols. Therefore this increase could simply reflect a natural development of the biobank review system.

In order to accommodate the increased number of amendments and reduce the number of items on the committee's agenda, in July 2018 the committee mandated the chair to review non-substantial amendments outside of the regular committee meetings. Non-substantial amendments are defined as amendments that do not constitute a change affecting one or more of the review criteria such that a new review by the committee is not needed. Due to this mandate, the committee's agenda remained manageable and the review times did not increase (section 5.4).

Amendments sub-biobank and release protocols

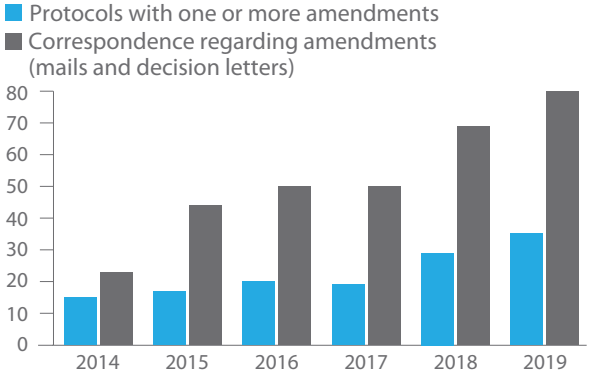

Figure 12. Number of protocols with one or more amendments per year together with the number of correspondence items regarding the review of those amendments, per year.

5.6 Correspondence

In 2019, the increased number of new submissions and amendments also resulted in an increase in the number of letters and e-mails sent by the office.

E-mails and letters sent out by BREC office increased

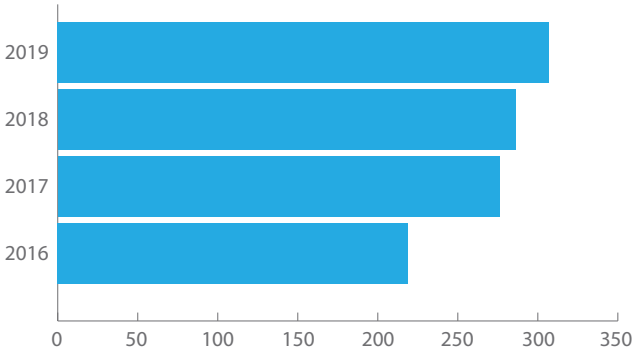

Figure 13. Total number of e-mails and letters sent out in 2019 by the BREC office regarding the review of sub-biobanks, release protocols and amendments to both types of submissions, compared to previous years.

5.7 Incidental findings

The TCBio SOP Notification of incidental findings, available on de committee's intranet pages, requires incidental findings to be submitted to the committee for review. The committee considers all the relevant information and advises on the steps to be taken with regards to return of the result if applicable. In 2019 for one release protocol a notifications of an incidental finding using human tissue for medical research was received. This case concerned a finding of a mutation related to the disease that is the subject of the biobank in which the donor participates. The committee advised that as the finding is related to the disease under study it is assumed that the biobank has a policy when a finding is clinically relevant and that when this is the case the finding is returned to the donor as promised in the information leaflet.

5.8 Final reports of study results

When a release protocol is approved, the applicant is asked to submit a final report within one year of completion of the study. In 2019, as in previous years, only a handful of final study reports have been received. To date there has been no active follow-up by the committee to ascertain the study results as it is the responsibility of the applicant to fulfill this requirement.

5.9 Submission procedures

Information and submission forms can be found on the intranet pages of the BREC on the UMC Utrecht intranet Connect: https://intranet.umcutrecht.nl/connect/onderzoek/biobank/Paginas/Toetsingscommissie-Biobanken.aspx

The forms and templates have been developed to facilitate review as laid down in the UMC Utrecht Biobank Regulations and continue to be improved in order to facilitate a rapid review process.

In addition, the office staff is available daily by e-mail and by phone for questions about the review process. Also, twice a week the office can be visited for questions without a prior appointment.
Background information regarding the importance of biobank ethics review is provided on the home page. Subpages provide information, forms and templates on each specific procedure (biobank establishment and release protocols). In order to facilitate external access to the information on the BREC procedures, preparations started in 2019 to construct a new BREC website on the UMC Utrecht corporate website.

As biobanks are long term infrastructures it is important that children, when they reach the age at which they themselves can decide about their participation in the biobank, are given the opportunity to exercise this right. At the start of their participation, the sub-biobank promises to send them a letter to remind them about this right when they turn 16. To help sub-biobanks carry out this task, a model recontact letter was drafted in 2019. The original sub-biobank information leaflet that provides the details about the specific sub-biobank is added as an attachment. The WKZ children's advisory board comprising of children of different ages, advised on the legibility of the model letter for the intended age group. This is an nice example of patient participation.

To facilitate non-Dutch speaking researchers, in 2019 English versions of both the sub-biobank protocol and the release protocol were made available on the English section of the BREC pages on Connect.

Chapter 6

Appeal against committee decisions

No formal appeals were received. However for one of the two rejected proposals (see 5.2.2 Outcome release protocol reviews) new information was provided in a newly submitted release protocol. Based on the new information, the committee concluded that the use of the human material could provide useful insights for scientific research and approval was given.

Chapter 7

Other committee activities

Besides the reviews under the UMC Utrecht Biobank Regulation reported above there are no other review activities to report for 2019.

Chapter 8

Requests for information under the Freedom of Information Act (Wob-verzoek)

In 2019, as in previous years, no requests for information regarding committee review procedures were received under de Freedom of Information Act (Wob-verzoek).

Chapter 9

Internal quality assurance and training

Generally, once or twice a year, the committee's secretary is asked to explain the UMC Utrecht biobank policy and review procedures by giving a presentation to UMC Utrecht employees. However, in 2019 no such presentations took place.

In November 2019, the **annual meeting** of the MREC was again held jointly with members of the BREC. During the annual meeting relevant developments regarding research ethics and national and or international regulations are discussed. Attendance facilitates training of TCBio committee members.

The 2019 topic: *Review of storage and use of human tissue for research*.

Presentations were held by

- prof. dr. J.J.M. van Delden (UMC Utrecht): *Ethical aspects of storage and use of human tissue for research: what has been accomplished and which questions remain?*
- dr. C. Smit (patient advocate): *Governance of biobanks: can ethical committees up with the pace of patient participation?*
- drs. M. Meershoek (Senior Policy Advisor Ethics, Ministry of Health): *Governance of human tissue for research: preliminary design of the Control of Human Tissue Act*

Attachment 1

Committee members and office staff in 2019

Committee members

Prof. J. (Hans) J.M. van Delden MD Ph.D. (ethicist, chair)	
Mr M. (Martin) Bootsma Ph.D. (epidemiologist)	
Mrs. B. C. (Claire) Collins LL.M. (lawyer)	From Nov 2019
Prof. R. (Roel) Goldschmeding MD Ph.D. (pathologist)	
Mrs D.A.H. (Dennie) Gullikers-Schoonderbeek, BSc (privacy officer)	From June 2019
Mr I. (Imo) Höfer MD Ph.D. (physician/scientist)	
Mr W. (Wigard) P. Kloosterman Ph.D. (geneticist)	Until March 2019
Mrs G.E.T. (Geranne) Lautenbach LL.M. Ph.D. (lawyer)	Until Nov 2019
Prof. T. (Tim) Leiner MD Ph.D. (radiologist – deputy chair)	Until July 2019
Mrs H.E. (Titia) van Lier LL.M. M.A. (on behalf of donors)	
Mrs G. (Gaby) V. Minasian LL.M. (lawyer)	From Nov 2019
Mr F.(Firdaus) A.A. Mohamed Hoesein MD Ph.D. (radiologist)	From July 2019
Prof. J.K.(Hans Kristian) Ploos van Amstel Ph.D. (geneticist)	From July 2019
Mrs S. (Susanne) Salomé-Kempjes LL.M. (privacy officer)	Until March 2019
Mrs N.A. (Kiki) Tesselaar Ph.D. (immunologist)	
Mr P.M.J. (Paco) Welsing Ph.D. (epidemiologist)	From July 2019

Substitute members

Mrs C (Caroline) van Baal Ph.D. (substitute epidemiologist)	Until Dec 2019
Prof. A. (Annelien) L. Bredenoord (substitute ethicist)	
Mrs I. (Irene) E. de Bruijne (on behalf of donors)	
Mrs A.(Alexia) M. Franse LL.M. (substitute lawyer)	
Mrs A.M. (Jenny) Zijlmans LL.M. (on behalf of donors)	

Office employees Department of Research Review 2019

Mrs M. (Marion) Berk-van der Linden Administrative employee	
Mrs N.M. (Nina) Beusmans LL.M. Senior Review procedure coordinator	
Mr V. (Vincent) Bontrop M.Sc. Senior Review procedure coordinator	until 1-12-2019
Mr R.P. (Rutger) Chorus M.A. Senior Review procedure coordinator	
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Attachment 2

Abbreviations

MERC	Medical Ethics Research Committee
WMO	Research involving Human Subjects Act (Dutch: Wet medisch-wetenschappelijk onderzoek met mensen
Wob	Freedom of Information Act (Dutch: Wet openbaarheid van bestuur)
BREC	Biobank Research Ethics Committee (Dutch: Toetsingscommissie Biobanken)

Colofon

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