UK Biobank Ethics and Governance Council
Forty-first Meeting

Meeting at Medical Research Council
One Kemble Street, London, WC2B 4AN

Monday 8 December 2014 at 10.30am

Agenda

1. **Apologies**

2. **Minutes** of fortieth meeting held on 9 September 2014

3. **Matters arising**
(i) Tracking of requests to UK Biobank
(ii) Subgroup reporting: Access oversight role
(iii) Subgroup reporting: Access meeting
(iv) Subgroup reporting: Revision of the EGF (feedback and linkage)

4. **Funders' review of the EGC**

5. **Dementias Platform UK** (Professor John Gallacher, Director DPUK and Dr Catherine Moody, MRC)

6. **Closed discussion on topics to discuss under item 7**

7. **Update from UK Biobank** (Professor Rory Collins, Chief Executive Officer)
(i) Report on access applications
(ii) Review of the access process
(iii) Imaging
(iv) Revision of the EGF
(v) Health outcome linkage and adjudication report
(vi) Participant and public involvement biannual report
(vii) IT and data security biannual report
(viii) Any other developments and outstanding recommendations from EGC40

8. **Closed discussion of matters arising under item 7**

9. **Expenditure report 2013/2014 and approved budget 2014/2015**

10. **Communications activities (including conference outcomes)**

11. **Report on meetings attended**
(i) Parliamentary Office of Science and Technology meeting 'Big Data and Governance: balancing risks and rewards' (06/11/14)
(ii) UK Biobank's participants' meeting (18/11/14)

12. **Any other business**

13. **Date of next meeting** 9 March 2015, Wellcome Trust

UK Biobank Ethics and Governance Council
Forty-first Meeting

8 December 2014
Medical Research Council, London

Present: Professor Roger Brownsword (Chair), Mr Andrew Russell, Professor Nils Hoppe, Professor Kate Hunt, Professor Søren Holm, Mrs Margaret Shotter, Dr Jonathan Hewitt, Dr Susan Wallace and Mr David Walker.

In attendance from EGC Secretariat: Ms Adrienne Hunt.

Observers: Dr Natalie Banner (Wellcome Trust) and Dr Jon Fistein (Medical Research Council) for the whole meeting. Ms Katherine Littler (Wellcome Trust) for item 4 only (by phone).

Speakers: Professor John Gallacher (Director, Dementias Platform UK) and Dr Catherine Moody (Medical Research Council) for item 5. Professor Rory Collins (Principal Investigator and Chief Executive, UK Biobank) for item 7.

1. Apologies

Apologies were received from Dr Sheelagh McGuinness, Ms Tracey Phillips and Mr Jonathan Sellors.

The Chair welcomed Dr Natalie Banner, who is acting as the Wellcome Trust observer during Katherine Littler's maternity leave.

2. Minutes of fortieth meeting held on 9 September 2014

The Council approved the circulated minutes.

3. Matters arising

Tracking of requests to UK Biobank

Members noted the outstanding requests to UK Biobank.

Subgroup reporting: Access oversight role

Over recent months a new three strand access oversight governance model has been developed comprising (i) alerting, (ii) reporting, and (iii) auditing (see Annex A). Members reviewed a final draft which clarifies that the EGC will take commissioning and financial responsibility for the audits.

Members approved the new model which will be adopted on January 1, 2015.

Subgroup reporting: Access meeting

Members received a written report of the 8 September meeting between members of the EGC access subgroup and Dr Tim Peakman (UK Biobank's Deputy Chief Executive Officer), Mrs Lorraine Gillions (Research Access Administration Manager) and Ms Erin Scobie (Access Administrator).

Subgroup reporting: Revision of the EGF (feedback and linkage)

In recent months, two small group discussion meetings have taken place at which revision of the Ethics and Governance Framework (EGF) was discussed: (i) In October, Professor Rory Collins, Mr Jonathan Sellors, Professor Mike Parker and the EGC Chair and Secretary met to discuss how to handle requests from other research resources to link data on individuals who are participants in both studies. One conclusion from that meeting was that the EGF should be augmented with a suitable protocol by which UK Biobank would consider issues that do not fall within the literal wording of the participant consent and EGF. (ii) In December, representatives from UK Biobank, the EGC and funders met to discuss revision of the EGF more broadly.

Between these two meetings the Secretary invited members' input on what aspects of the EGF require revision; nearly 60 comments were received ranging from mechanical to substantive points and these have since been sent to UK Biobank.

4. Funders' review of the EGC

The Review Panel will meet on the 17 February to interview key stakeholders and to consider the evidence.

Given the complexity of the governance structure, and the desire to elicit in-depth opinions, the funders have decided to commission a number of focus groups with UK Biobank participants. Commencing in January, this work will explore participants' views on the current and future role and activities of the EGC.

Members proposed amendments to the EGC's draft submission; the final submission will be sent to the funders before January 12.

The EGC will be advised of the outcome of the review in late April/early May.

5. Dementias Platform UK (Professor John Gallacher, Director DPUK and Dr Catherine Moody, MRC)

Professor John Gallacher (Director of the Medical Research Council (MRC) Dementias Platform UK and a member of UK Biobank's Steering Committee) presented an overview of the MRC Dementias Platform UK (DPUK). DPUK is 'a multi-million pound public-private partnership, developed and led by the Medical Research Council, to accelerate progress in, and open up, dementias research. The

aims of this major initiative are early detection, improved treatment and, ultimately, prevention of dementias'.[1]

DPUK will bring together 22 existing cohorts, creating a platform of two million participants aged 50 and over including people from the general population, people known to be at-risk of developing dementia and people diagnosed with early-stage dementia. UK Biobank is at the heart of DPUK; the Platform will draw on the range of information held by UK Biobank including genetic, lifestyle, imaging and the answers to the cognitive function questionnaire (which Professor Gallacher developed).

This is the first case of UK Biobank becoming a central part of a much larger study, giving rise to questions about how the two initiatives will relate in terms of their governance structures, data sharing arrangements and access mechanisms and how the relationship between the initiatives will be communicated to UK Biobank participants. Professor Gallacher's presentation was very informative and the discussion mutually valuable. We anticipate that there will be further interactions and discussions as DPUK develops.

6. Closed discussion on topics to discuss under item 7

Members agreed on a number of matters to raise with Professor Collins.

7. Update from UK Biobank (Professor Rory Collins, Chief Executive Officer)

Report on access applications

There has been a significant increase in applications, in particular requests for genotyping data. There has also been an increase in non-UK applications; the Frontiers meeting may have played a part in this, but it could also be the availability of the resource spreading by word of mouth.

Members asked whether there is an optimum use of the resource and whether UK Biobank has any formal targets. UK Biobank aims to encourage extensive and appropriate use of the resource; in particular Professor Collins would like to see more commercial and non-UK use. Recent appointments to the Board of Directors included a colleague from industry (GSK); it is hoped that this new member will help raise the profile of UK Biobank in the commercial sector.

There are a number of routes by which UK Biobank data and samples might be turned into information for use by the research community, including through the work of third party researchers. For example, UK Biobank has collaborative agreements with a number of research groups to undertake analysis of certain data sets (e.g. imaging, accelerometer and nutrition data). Under this scheme there is no preferential access to the resulting information but the researchers could write a paper on the algorithm generation. Alternatively, a third party researcher could make

[1] www.mrc.ac.uk/research/facilities/dementias-platform-uk

an access application, an example here is the UK BiLEVE project which has genotyped 50,000 UK Biobank participants. In this situation the researcher can use the data and samples for a specific research project and then return the resulting information to UK Biobank for use by others. If the researcher would like to use the information for a further purpose this would require a new application to be submitted.

Review of the access process

The November Access Sub-Committee (ASC) meeting included a discussion on how UK Biobank might streamline the access process, in particular for certain types of application (e.g. data only). Mr Sellors will prepare a report on the streamlining of the access process and this will be made available to the EGC.

Imaging

UK Biobank has now demonstrated that it can image 18 participants per day. The funders have asked UK Biobank to run at this capacity for the next 6/7 months to show that the attained rate is feasible over the long term. The aim is to recruit 6-8,000 participants by July 2015.

A 24% attendance rate has been achieved, with participants mostly being drawn from the area surrounding the assessment centre. Recently, UK Biobank has recruited from further afield and found a substantial drop in the attendance rate when the travel time exceeds 2 hours.

An attendance rate of 20% is required for the project to recruit 100,000 participants. Under the current conditions (i.e. with the fall-off in attendance rate mentioned above and the prevailing exclusion rate) the proposed 3 centre model would not be able to recruit the target 100,000 participants. However, measures are being investigated to achieve the target. First, the exclusion rate could be reduced (half of the exclusions are due to recent joints/implants which, rather than there being a safety issue for the participant, have an impact on the DEXA scan). Secondly, participation could be increased by providing transport to and from the assessment centre, by reminders and by increased communications activity. Finding ways to keep the 3 centre model is preferable to opening a 4th centre; it would take at least 3 months to relocate the imaging facility and be costly.

Detailed quality control of the images is now taking place and UK Biobank is also assessing whether cross sectional analyses can be performed (e.g. comparing APOE4 genotype with brain images and measures of cognitive function). The results will be used to demonstrate to the Review Panel the ways in which the data can be interrogated.

UK Biobank's Main Phase funding proposal will be submitted in July 2015 with a view to imaging 100,000 participants (the assessment centre will continue to operate during the review period). During the development of the Main Phase proposal, considerations will be given to the non-imaging measures and which of these should

be incorporated into the visit. UK Biobank will also decide what additional measures to include in relation to the Dementias Platform UK (DPUK, see Item 5).

It is anticipated that, in time, approximately 10,000 imaged participants will be invited to have repeat imaging as part of the DPUK. Members asked whether UK Biobank's imaging consent materials will mention the DPUK and UK Biobank's involvement in the initiative. Professor Collins advised that while only a minority of imaged participants will be invited back, and given that this further imaging would be optional and require further consent, it might be preferable to treat this as separate. UK Biobank has provided general information to participants about DPUK, for example through a news story on its website. Professor Collins noted that at the end of the imaging pilot visit participants are asked if they would be willing to be invited back for a further assessment and over 90% said yes.

Incidental findings protocol

Approximately 19% of the scanned participants have received feedback relating to at least one imaging modality as a result of the systematic review of the images of the first 1,000 imaged participants by specialist radiologists[2]; some participants have received feedback on more than one modality. A critical element of the pilot is a qualitative and quantitative study that will assess the attitudes of participants to receiving this feedback and track whether these attitudes change over time.

The first qualitative assessment with participants took place earlier this week, with further assessments planned for the New Year. The 6 week questionnaire data have been reviewed; there is a lot of uncertainty about the outcomes for participants at this stage. A clearer picture of the outcomes should emerge from the 6 month questionnaires and follow-up through the participants' health records.

Revision of the EGF

Professor Collins confirmed UK Biobank's plans for revision of the EGF and the proposal to create a dynamic document with hyperlinks to supporting information (e.g. more detailed policies and procedures that are regularly updated and/or videos).

Health outcome linkage and adjudication report

Members received a report outlining UK Biobank's progress in relation to health record linkage, and in particular its approach to seeking access to primary care records (working with data providers to establish an opt-out system for general practices (GPs)). This approach is supported by the Royal College of GPs.

Professor Collins also provided an update on UK Biobank's work to collect data from participants directly via web questionnaires. Data from the cognitive function

[2] The systematic review is being undertaken in order to evaluate the proposed incidental findings feedback protocol whereby any potentially serious findings that happen to be noticed by the radiographer, and that are subsequently verified by a radiologist, will be fed back to participants and their general practitioner. The two processes are running in parallel and are blinded to each other.

questionnaire should be added to the database in the first quarter of 2015. An occupational history web questionnaire is planned for spring 2015, while a mood/mental health questionnaire should be sent out towards the end of 2015.

Participant and public involvement biannual report

UK Biobank recently held its first participants' meeting in Edinburgh. The event was significantly oversubscribed, resulting in UK Biobank deciding to hold a further event in the city in the New Year. Having proved the concept, and in light of the high level of interest and engagement by participants, UK Biobank will hold participants' meetings on a regular basis in future. The EGC fully supports the extension of this engagement work as one element of UK Biobank's communications strategy.

Professor Collins reported that there seems to be a changing attitude to UK Biobank spreading, perhaps, by word of mouth. For example, there has been an increasingly positive response from participants to the activity monitors; the initial response rate was 40% and this is now 55%. The monitors are being sent out randomly and so it is unlikely that this change is due to bias.

UK Biobank will inform participants about the changes to the EGF in a proactive way, for example notifying participants by email. On this point, Professor Collins raised an equity of access issue; UK Biobank has email addresses for the majority but not all participants. While the annual newsletter is sent out both electronically and in hardcopy (to participants with no email or where the email bounces), other opportunities are communicated by email only. A member suggested that UK Biobank could – when sending out the hard copy annual newsletters – ask whether the participant would like to nominate someone who has an email address to receive their UK Biobank communications.

IT and data security biannual report

Members reviewed the new-look report that now includes (i) a schematic of data flows between the various organisations that process and/or store UK Biobank data and (ii) a tabular presentation to show where UK Biobank is up to in relation to ISO accreditation status, penetrance testing etc.

During the discussion, Professor Collins confirmed the formal responsibilities for data security at UK Biobank and in the third party organisations that hold data on behalf of the project (e.g. the Clinical Trial Service Unit and Cardiff University). Professor Collins proposed to look into the possibility of undertaking an external audit of the Cardiff University systems that deal with UK Biobank data (noting that only an internal audit has taken place to date).

Any other developments and outstanding recommendations from EGC40

Genotyping: Release of the first tranche of data for 150,000 participants will take place in the first quarter of 2015. The Wellcome Trust Centre for Human Genetics will impute 50 million markers by combining the 820,000 measured genotypes with

reference sequence data; imputed data relating to the first tranche of genotypes should be available by May 2015.

A method has been established by which the genotyping data can be compressed, allowing transfer to researchers over the internet. This mitigates the need for a dedicated environment where researchers could interrogate the data remotely; this option was being considered but building such an environment is a substantial undertaking. The transfer of compressed data is non-trivial but is realistic.

UK Biobank aims to make genotype information available for all 500,000 participants by the end of 2015. It is hoped that imputation data (including re-imputation of the earlier data set) will be available shortly after.

Assessing arrhythmias: A small scale study in about 100 imaged participants is being planned to test the feasibility and acceptability of prolonged cardiac monitoring. In light of this experience, a grant proposal will be submitted involving 20,000 participants being asked to wear a monitor (akin to a large plaster) over a two week period.

Enhancement Working Group: The International Scientific Advisory Board met in November and, amongst other things, recommended that the Enhancement Working Group should be reconvened. Professor Paul Elliott has agreed to return as chair of the Group; discussions will include the possibility of more detailed assays, including proteomics, and environmental exposures.

8. Closed discussion of matters arising under item 7

Reflecting on UK Biobank's intention to hold further participants' meetings in future, members agreed to ask UK Biobank whether it plans to capture and in any way use the views expressed by participants at these meetings.

9. Expenditure report 2013/2014 and approved budget 2014/2015

Members noted that the total spend on EGC operations in 2013/2014 was £92,440, 93% of the budget. A budget of £149,012 has been approved for 2014/2015; the increase relates to the costs of the EGC 10-year anniversary conference.

10. Communications activities (including conference outcomes)

In November, to mark its 10-year anniversary, the EGC held a public lecture and two day international conference. The purpose of the conference was to share lessons learnt from the EGC's experience and to identify and discuss upcoming challenges in biobank ethics and governance.

The conference attracted 110 delegates from a broad range of countries and biobanks, including delegates from Iceland, Taiwan, the UK, Sweden, the United

States of America, the Netherlands, Norway, Germany, Italy, Singapore, the Czech Republic, Japan, Canada, Austria, France, Estonia, Finland and Denmark. There was a high level of interest and engagement throughout the event and positive feedback was received both during and after the event.

A full conference report will be published, in addition to a summary in the Annual Review 2014. The conference presentations will be made available online.

11. Report on meetings attended

Parliamentary Office of Science and Technology (POST) meeting 'Big Data and Governance: balancing risks and rewards' (06/11/14)

The EGC Secretary attended this meeting which drew on POST's 'suite of work on 'big data', investigating the opportunities and challenges it presents in fields such as business, healthcare, transport, energy, and crime and security, as well as the issues it creates for governance'[3]. A POST Note on biobanks was prepared as part of this work[4].

UK Biobank's participants' meeting (18/11/14)

Members noted an informal report from the EGC Secretary who attended UK Biobank's first participants' meeting.

12. Any other business

The question of open access publications arose during the day, in particular whether all researchers who use UK Biobank should be mandated to publish in an open access journal. During this item the funders confirmed that while they have open access policies, they cannot mandate open access publishing for research that they do not directly fund. It was pointed out, however, that in part the Wellcome Trust and Medical Research Council (and UK Biobank's other funders) are resourcing all researchers who use the resource by funding UK Biobank to make the data and samples available.[5]

13. Date of next meeting 9 March 2015, Wellcome Trust

[3] www.parliament.uk/mps-lords-and-offices/offices/bicameral/post/post-events/big_data_and_governance
[4] www.parliament.uk/briefing-papers/POST-PN-473/biobanks
[5] Post meeting note: UK Biobank's access procedures require that 'The applicant PI is required to use their best endeavours to publish the findings of any research deriving from the Resource in an academic journal or on an open source publication site within 6 months after the date when it was agreed that the research would be completed.' Section C11.1

Annex A The Ethics and Governance Council's Oversight in Relation to UK Biobank's Administration of the Access Process (Final 13/11/14)

Context

In Spring 2012, UK Biobank opened its resource to researchers. Since that time, the Ethics and Governance Council (the EGC) has exercised its oversight responsibilities with regard to access to the resource in three principal ways: first, it has made extensive use of the Level B 'real-time' access that it has to applications; secondly, it has received quarterly reports from UK Biobank with regard to the top-line figures – in particular, the number of registrations and applications, whether applicants and applications come from the academic or commercial sector, whether they come from the UK or from overseas, and so on; and, thirdly, in accordance with the requirements of the Ethics and Governance Framework, the EGC has commented on applications that request re-contact with participants.

Given this experience, both UK Biobank and the EGC now have a much clearer idea of the kinds of ethics and governance issues to which applications might give rise as well as the numbers of applications that are problematic in this respect. Thus far, it seems that many applications do not raise any significant ethics or governance issues; these are applications that are now regarded as relatively 'routine'. However, there are some applications that give rise to issues that were anticipated and that need to be addressed by the EGC (for example, concerning re-contact) as well as applications that raise novel ethics or governance issues and that need to be given careful consideration by both UK Biobank and the EGC.

In this context, it is agreed that the time is right to modify the way that the EGC exercises its oversight. In place of the current arrangements, it is agreed that the EGC's oversight should be operated in accordance with a three-stranded model that brings together elements of alert, report, and audit.

Guiding Principles

The elaboration of the three-stranded oversight model is guided by the following principles:

- Robustness: given the EGC's responsibility to ensure that access decisions are made in a way that respects both the interests of participants and the larger public interest, the arrangements for its oversight must be sufficiently robust to enable it to discharge this function and to do so in a way that maintains the confidence of all stakeholders in UK Biobank.
- Transparency: as a corollary of the requirement of robustness, the EGC must always have the right to inspect any aspect of the access process.
- Workability and proportionality: given that applications need to be processed expeditiously, the arrangements for oversight should make only such demands of UK Biobank as are reasonable and proportionate.
- Efficiency: for both UK Biobank and the EGC, it is important that limited resources are used in the most efficient way; ideally, this means that time and attention should be focused on those applications that raise difficulties, rather than those that are straightforward.

The Three-Stranded Model

The agreed oversight model has three principal elements: Alert (by UK Biobank to the EGC); Report (by UK Biobank to the EGC); and Audit (by a third party, for the EGC, and to be shared and discussed with UK Biobank).

ALERT

The principal feature of alert is that UK Biobank will assume responsibility for alerting the EGC to applications that raise ethics or governance issues that merit the Council's attention. Under this arrangement, the EGC will rely on UK Biobank to advise it that a significant application is in the system. An application will be significant where it involves:

- a request for re-contact; or
- a novel and/or important ethical issue; or
- a novel and/or important governance issue; or
- making a decision that will set a major precedent; or
- some other matter that, in the judgment of UK Biobank, merits the attention of the EGC.

In such cases, UK Biobank should alert the EGC at the earliest opportunity. If in doubt about the significance of an application, UK Biobank should err on the side of caution and alert the EGC. When UK Biobank alerts the EGC, along with the alert, it should send the EGC a copy of the full application (or enable electronic access to the full application).

Initially, the question of when and how the EGC should respond to an alert will need to be resolved case-by-case. In some cases, UK Biobank will expressly invite the EGC to respond within a particular time-scale; in other cases, the EGC might set its own time-frame for responding; and, in some cases, the best way to proceed might be by discussion in a small joint working group (drawing on both UK Biobank and the EGC).

REPORT

UK Biobank should report on the access process at each quarterly meeting of the EGC.

The report should include the following:

- the usual top-line figures; and
- the Access Sub-Committee Minutes and Record of Decisions; and
- details of applications that, even if not 'significant' (in the sense that they will have been the subject of an alert), are in any way 'salient'; and
- details of applications that have been rejected.

AUDIT

Within a reasonable time after the new system has been in operation, an audit should be conducted to check that UK Biobank is dealing with access applications in accordance with the spirit and letter of this oversight arrangement.

Thereafter, unless an audit recommends otherwise, audits should take place every three years.

The EGC would commission the audit and have input into the terms and conduct of the audit; but the auditors will be drawn from outside the EGC. The audit report would be envisaged as being prepared for the EGC, then to be shared and discussed with UK Biobank.

Commencement

It is agreed that the new oversight model should be put into practice as from January 1, 2015.