DIRECT Consortium

Data Access Policy

Version 5, September 2020

DIRECT Project

Policy for sharing materials and accessing Data

In order to conduct the research planned within DIRECT, researchers require access to Data and samples generated or contributed by DIRECT Participants. Given the size of the consortium and the variety of different work packages and studies it involves, there needs to be a clear set of policies for how these samples and Data are collected and stored within DIRECT and how they are transferred between researchers to ensure:

- all members of the DIRECT consortium are able to access the Data and materials they need,
- the research fits with the consent that has been given by patients/research subjects,
- the requirements of the General Data Protection Regulation (GDPR) are met
- Research can progress without unnecessary delay
- To enable access to the data and samples by users external to the DIRECT consortium.

This paper sets out the policies and processes for sharing materials and accessing Data within the DIRECT consortium.

It covers:

1. Description of the DIRECT Database and the DIRECT Computerome

All Data generated in the DIRECT Project as well as key Background Data will be stored in a database (the DIRECT Database). The DIRECT Database was custom built for the DIRECT consortium by Søren Brunak's group at the Technical University of Denmark (DTU). The DIRECT Database is a relational database that runs on MySQL and has a tailored interface that is mainly used for data entry and limited data query and download functions.

The database server is stored in a room with restricted access and added protection against physical intrusion. Access to the server for Data entry is possible only through a secure,

encrypted protocol between the server and the Data Entry Clients (https). Only users cleared for Data entry can access this functionality by username and password. The DIRECT Database Manager at the DTU is responsible for the administration of DIRECT Authorised Personnel for DIRECT Database access and for their protected login data. The DIRECT Database User Interface is mainly used for Data entry and can be accessed at the following URL: https://directweb.cbs.dtu.dk/.

Data Analysis in the DIRECT project is carried out on a separate, secure cloud, the Computerome High Performance Computing (HPC) Unix server (CentOs Lunix ver.7.0) with a standard set of Unix tools. Statistical software and other necessary software are installed by the DTU team in collaboration with the Computerome team as appropriate.

Access to the Computerome system is limited to named individuals sanctioned by the Samples and Data Access Committee (SDC) under the authority of the Management Board (MB) or its successor the DIRECT Legacy Board (DLB). It functions via a two-factor CITRIX installation with SMS passcode or Authenticator confirmation (authentication is done through a password and a one-time passcode sent through an SMS or via the Google / Microsoft Authenticator systems). All communication between the user and the CITRIX system is through an SSL connection with 128-bit encryption. No Data can be exported from the Computerome machines through the CITRIX installation, nor is the Computerome connected to the internet.

The Data Access Policy allows limited downloads from the Computerome. If and when approved by the DLB, data are downloaded via the DIRECT database web interface over a secure transfer protocol. All downloads are logged in the database, and the users are required to review and agree to the established rules of data download. Through the same interface, users can upload data to the Computerome (e.g. scripts to analyse data).

2. The Sample and Data Committee (SDC)

Under the direction and overall authority of the DLB the Sample and Data Committee (SDC) is responsible for the development of policy, and for approval and oversight of access to Data. The SDC committee thus has delegated responsibilities from the DLB and is directly responsible and accountable to the Board for its activities.

2.1 Sample and Data Committee (SDC)

2.1.1 Composition

Jane Kaye (Chair) or her deputy Miranda Mourby	WP9 DIRECT Project Lead; UOXF
Ian Forgie	DIRECT Programme Manager; UNIVDUN
Konstantinos Tsirigos	DIRECT Database Manager; DTU
Bernd Jablonka	DIRECT Consortium Manager; SAD
Giuseppe 'Nick' Giordano	WP2 DIRECT Project manager; ULUND
Tim McDonald	DIRECT Central Laboratory; UNEXE

2.1.2 Responsibilities

The main functions of the SDC are to develop and provide guidance on policy and triage requests for access to data or samples on behalf of the DLB.

Developing Policy

The SDC will develop policy relating to Samples and Data within the DIRECT project, including updating and reviewing the policies described within this paper. Policy will be developed alongside assessment of the ethical, legal and regulatory requirements of the project and will draw upon current best practice.

As part of the process for developing policy, some issues will be discussed with patient groups, who will assess their significance and acceptability. Patient engagement will provide a useful opportunity to get broader input into policy development. This will be particularly relevant when discussing issues relating to translational research and personalised medicine.

Providing Guidance on Policy

The SDC will provide the forum for queries that do not appear to be covered under current policies, and will advise DIRECT Consortium members on any grey areas. Where this concerns the interpretation and application of policy, any conclusions will be fed back into policy development. Ultimately all policy regarding data or sample handling and security will be agreed by the Management Board or its successor the DLB.

Meeting and Reporting

The SDC committee will hold periodic teleconferences to discuss issues arising. Outcomes of these meetings will be reported to the DIRECT Legacy Board. DIRECT Consortium members should contact Jane Kaye (jane.kaye@law.ox.ac.uk) or any other member of the SDC if they have queries or issues that they would like the SDC to discuss.

2.1.3 Triaging by the SDC.

A three-tiered process of the SDC will enable requests from members of the DIRECT consortium for access to Data held within the DIRECT database (usually via the DIRECT Computerome) to be assessed and processed quickly and efficiently.

Tier 1: Processing of Data Access request Forms (DAF), collation and recording of DIRECT Data Access SOP signatures and triaging initial requests for access to DIRECT Data.

A sub-set of the SDC, normally the Programme Manager, will approve straight-forward applications that are clearly within the scope of DIRECT (see annex IX), such as the inclusion of a new researcher from one of the institutions participating in the consortium who wishes to join an existing analysis team and adding their name to an existing DAF. More complex requests will be referred to the wider SDC.

In instances where access has been approved, the Programme Manager will assign a reference number to the DAF, and return it to the researcher(s) to notify them of the decision. The approved request will be forwarded to DTU who will be responsible for setting up accounts and providing access to the required folders on the Computerome.

Tier 2: The wider SDC will, in consultation with the Academic Lead and appropriate other Work Package Leads, consider any unusual or non-standard access requests and determine whether access will be granted to the DIRECT Database via the Computerome (e.g. including confirming whether a request falls outside the scope of the DIRECT project) or whether the request should be referred to the full DLB for consideration

Tier 3: All new Analysis Plans (whether internal or from an external party) will, after presentation to the Analysts and Principal Investigators, be put before the DLB for review and approval. In addition, for any new internal Analysis Plan or data or sample access request, if there is a difference of opinion between the requesting researcher and Work Package (WP) leads, or between WP leads, as to the appropriateness of the request, the matter will be referred to the full Management Board or its successor, the DLB for adjudication.

The SDC will complete the relevant section of the DAF, including assigning a reference number, and return it to researchers to notify them of the outcome of the request. In instances where access has been approved, the SDC will forward the approved request to the DTU, which will provide access to the required Data.

2.2 Meeting and Reporting

A record of all Data access and download requests, including the outcome of the request, will be held and provided to the Management Board / DIRECT Legacy Board when required.

Once the Analysis Plan has been reviewed by the Analysts and PI group and approved by Management Board / DIRECT Legacy Board, the analysis team lead will, in conjunction with a DAF, liaise with the SDC and DTU to determine which data are required.

3. Submitting Data to the DIRECT Database

Each researcher uploading Background Data to the DIRECT Database must complete a Data Submission Form (DSF) (following the SOP, see annex II) outlining the dataset to be uploaded. This form is sent directly to the DTU and provides the opportunity for the researcher to stipulate any restrictions (e.g. relating to consent or legislation) on the future use of Data by DIRECT Participants.

Researchers wishing to import prospective Data from another database, either as a specific Data file or in another format other than as individual level Data submitted by eCRF, must also submit a DSF to the DTU. This will ensure that the consortium has a detailed record of the Data that is available.

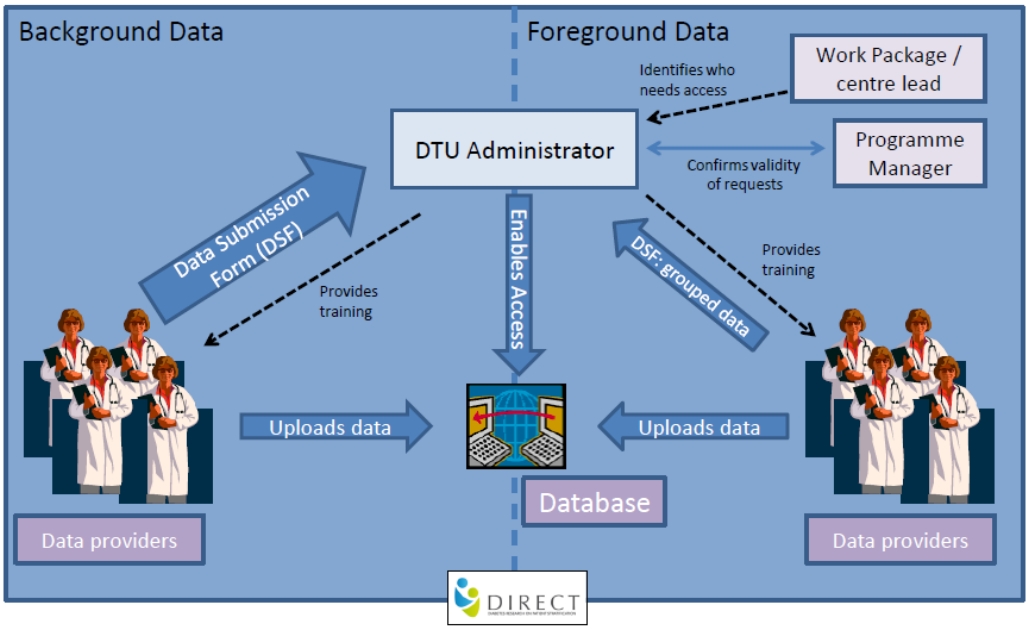
To submit individual-level foreground Data to the database, the Data Providers – usually the WP lead or centre lead, should contact the DIRECT Database administrator to notify that access is required, including a list of personnel who will be uploading Data. The administrator will confirm these requests with the Programme Manager. The DIRECT consortium members must provide written updates to the list of DIRECT authorised personnel to reflect any changes or departures in researchers who are involved in Data management or usage.

For both Foreground and Background Data, the DIRECT Database administrator will organise appropriate training for use of the database and will enable access for validated users.

Where possible, for prospective studies, data entry via the DIRECT Database is preferred because the web based (eCRF) system contains in-built Data clarification checks which will reduce the need for Data cleaning of both composite datasets.

The DIRECT Database User Interface provides limited access for all users to view the Data that they (but not other institutions) have entered (for example eCRF Data), as well as certain summary statistics. This is to allow users to check the integrity of the Data they have entered. Results from laboratory analyses can be viewed only by the laboratory personnel. Data exports from the DIRECT Database via the User Interface need to be approved by the SDC. Full audit trails of all database transactions are generated and stored so all actions performed on the database via the User Interface are tracked.

Figure 1: Submitting Data to the DIRECT database



4. Accessing your own Data, other groups' Data, or a mixture of both

All researchers wishing to access DIRECT Data need to sign a copy of the Data Access Standard Operating Procedure (annex IV) VERSION 2 to confirm that they have read and understood the Data Access Policy and terms and conditions for the use of Data within DIRECT. A copy of this form must be sent to the Programme Manager the first time a researcher requires access to DIRECT Data.

4.1 Data and sample Access Forms (DAF)
All researchers wishing to access Data stored on the DIRECT database must complete a Data and sample Access Form (DAF) (or, with the knowledge of the original submitter of an existing DAF, have their name added to that existing DAF). This form enables researchers to stipulate exactly to which Data they require access and will help the DTU provide a streamlined process for Data provision, which will make it quicker and easier for researchers to access the Data they need. These transparent and accountable management structures also ensure that the project conforms to legal requirements and good information governance standards.

Depending on the Data required, researchers need to include slightly different information on the DAF, as described below:

4.2 Researchers accessing their own Data
All researchers will be able to access Data that they have entered onto the DIRECT Database, for example eCRF Data, via the Computerome or as a download from the DIRECT Database. Researchers wishing to access their own Centre Data (described as own data for the purposes of access, with the understanding that consortium data is co-owned) will complete a DAF to specify which Data are required (including the work package and study, and types of Data).

If all the Data requested on the Data access form belongs to the requesting researcher/group, the researcher should tick the 'own Data' box, and send the DAF to the SDC who will arrange with DTU for the required Data to be uploaded onto the Computerome, or downloaded as required. It is not necessary for researchers to submit an Analysis Plan to access their own Data.

4.3 Access to composite Data
For researchers wanting to access a composite dataset, which includes for example Data they have uploaded (centre 'own Data'), sample analysis by other research groups, and/or other centres' individual-level Data, a DAF must be completed (following the relevant SOP, refer to annex IV) stipulating the research question and outlining the Data requested. The DAF should be accompanied by an Analysis Plan that has been agreed upon by the working group that will be conducting the research and approved by the Management Board / DLB.

4.4 Process for Analysis Plan approval
Analysis Plans can be proposed by any individual or partner in the consortium but generally are designed as part of working groups or work packages within the consortium. An analyst posing a research question should first consult the list of existing Analysis Plans to see which Analysis Plans have already been approved, and to determine whether there is an existing working group that might be relevant for the new research question. Following discussion with the working group lead, or having formed a new working group if required, the Analysis Plan should be developed within the working group. It is expected that the Analysis Plan is presented during one of the regular Analyst –PI calls or similar and discussed with the wider group, before being sent to the Management Board / DLB for approval.

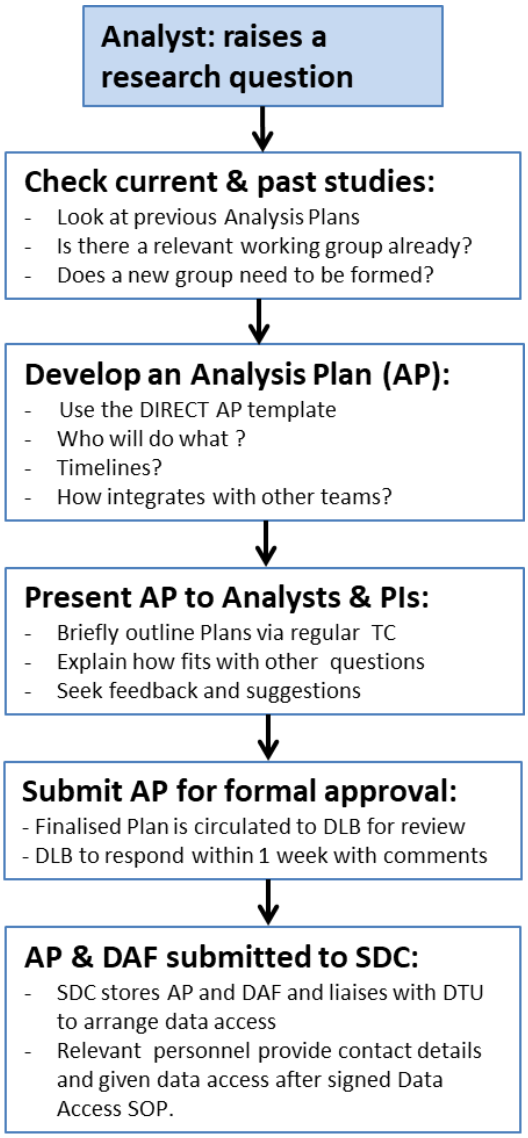
The basis for this approvals process is to ensure that the priority research questions for the consortium are being covered first, and to provide a good overview and coordination of who is involved in what. Discussing the Plan during the regular Analyst –PI calls first will help position the research in the context of other analyses being conducted and raise any relevant questions before consideration by the Management Board/ DLB.

This applies to requests for access to both Background and Foreground Data.

The Management Board / DLB will consider Analysis Plans that have been presented at an Analyst-PI call within 5 working days.

Once the Analysis Plan has been approved, an accompanying DAF is submitted to the SDC, who will process the request, (see Figure below: The SDC triage process for Data access requests). The SDC is not responsible for evaluating and approving the Analysis Plan but for ensuring the DAF is adequately detailed and in line with the approved Analysis Plan.

Figure 2: Process for Analysis Plan review and approval



4.5 Data and sample Request approval

The SDC should assess whether the research is within the scope of the DIRECT Description of Work (refer to annex IX for research questions). For requests that are obviously within the scope of the DIRECT project, approval will normally be expedited if the following conditions are clearly met:

- Timely
- Enabling collaboration
- Indicates scientist(s) who will do the analysis
- Indicates specific Data requested for analysis
- Outlines a robust research question with an Analysis Plan
- Outlines a robust method for analysis
- Is not in breach of any ethical, legal or regulatory requirements
- Fits clearly within a specific work package

For requests where there is any doubt as to whether the above criteria have been met, or any other concerns, the SDC will refer the request to the DLB. In all cases final approval rests with the DLB.

Once a request has been approved, the lead researcher will work with the SDC and DTU to determine exactly which data are required for the analysis. DTU will then provide the data from the DIRECT database and save it in the appropriate working group folder on the Computerome. This will allow all members of the analysis team to access the required data and to upload relevant analyses to that working group folder. Although researchers can be members of more than one folder researchers are not allowed to copy and share data from working group folders, or transfer data between folders. Once completed an 'Extraction Report' will be generated by DTU to act as a record of what was extracted. This report can be held with the Data Access Request.

Researchers should note that on receiving access to the requested data, it is possible they may be granted access to a wider dataset than they specifically requested. Researchers are trusted to select and access only the data they have requested, in line with the research outlined in the Analysis Plan. Without exception, researchers must submit a new request to the SDC for each new research question or Analysis Plan, or for any extension or development of an existing Analysis Plan, whether or not they coincidentally have access to the required data as a result of a previous request.

Access to data in line with submitted Analysis Plans will be monitored to keep oversight of the research that is taking place throughout the consortium, to ensure that all parties are supported in conducting high quality research to contribute to DIRECT, and that all partners have an opportunity to conduct research within the consortium in a fair and reasonable manner. Any instances where it is felt that this trust has been abused could limit future access to data and may lead to the introduction of a more stringent access procedure.

5. Accessing Data for Quality Control (QC) purposes

All prospective data collected on behalf of the DIRECT consortium is co-owned by members of the consortium, recognising that data generated by different members of the consortium

contribute to different aspects of the research pathway. Once data are uploaded onto the database, a data cleaning process is performed by the Data Quality Inspection Team (DQIT), to ensure that the dataset is as complete and as high quality as possible. If data is required for QC purposes, it is possible to submit an access request without an accompanied Analysis Plan. This should be clearly marked on the access request form. In these cases, data can only be accessed and used for QC, and must be deleted as soon as the QC process has been completed. If, as part of a QC process, access is required to the Computerome, without needing to access specific data, a DAF should still be completed to enable the database team to set up an appropriate account on the Computerome.

6. Accessing DIRECT Data for research outside the immediate scope of DIRECT

Where it is not clear whether the Data request is within the immediate scope of the DIRECT project, the SDC will refer the request to the DLB, for consideration by the Work Package leads. The DLB will have approved the Analysis Plan and thus the SDC's role is to check that the data requested fits with the Analysis Plan, and to assist in the administration of data access. If, however, the DLB or SDC considers a research question to be out of the primary scope of DIRECT, the DAF will be returned to the Data requester.

If members of the consortium wish to use DIRECT data for purposes outside the immediate objectives of DIRECT, this will need to be considered on a case by case basis, depending on the nature of the request. Data Analysis may be feasible on the Computerome. Alternatively it may be necessary to draw up a Data Transfer Agreement (DTA) to act as a formal agreement between the consortium and the requestor to enable research on Diabetes and related conditions outside the primary aims of DIRECT. This is similar to the process for requests to access DIRECT data by researchers outside the consortium.

The agreement would need to identify which Data were to be shared, and the conditions for transfer, including how data would be accessed (i.e. via Computerome or via other means).

<u>Important note</u>: In all cases without exception the planned research must comply with and be consistent with the terms and conditions of the Consent provide by DIRECT participants

7. Download of Data from the DIRECT Database

All Data analyses should take place on the Computerome and Data will rarely be downloaded from the Computerome. Data that can normally be downloaded (for example for the purposes of discussing or presenting research results or for publication) includes:

- scripts, results of analyses, graphs, tables, plots, images, presentations and pdf files.

In extenuating circumstances researchers may be able to download Data from the Computerome (see section 8). This will be possible only when:

- Accessing own centre Data.
- Downloading results from the Computerome, for example for publication.

- Downloading Data for analysis in certain specific circumstances (see below), for example if Computerome cannot support the software required. In these instances, researchers are required to provide a clear explanation for their requirements as part of the initial request for access, and the request will require approval from the Management Board/ DLB.
- Downloading code written on Computerome

As indicated above analysis should be undertaken on Computerome whenever possible. However, in exceptional circumstances Centres can apply to download (or receive) a copy of specific DIRECT raw data sets for specific analysis, for example when data analysis on the DIRECT Computerome is impractical for whatever reason. A clear justification for the request must be provided. Each application to download data locally must be reviewed and approved by the Management Board / DLB and must fulfil the following conditions:

- The data must pertain only to prospectively collected DIRECT cohorts WP2.1, WP2.2 and WP3.3
- A formal application should be made stating why the download is necessary, what the data will be used for, what analyses will be performed and who (the specific personnel) will perform them.
- A separate application should be made by each institution wishing to download data
- The applicant (normally the lead DIRECT consortium member for that institution) should sign a hard copy of the application to say that they will adhere to all international, local and DIRECT data governance rules required for personal sensitive data and to accepted good practice in terms of data hosting and security.
- The data must not be shared with third parties or combined with other external data.
- The approval will be time limited (maximum of 6 months) but renewable by application.
- The version of the data provided will be the latest 'data freeze'. An additional request will be required to receive any subsequent data freeze.
- Data must be destroyed at the end of the approval period and written and signed confirmation provided that this has been done.

All downloads are recorded and are traceable to ensure this facility is not abused. Failure to comply with this policy may result in sanctions against the individual and their institution.

Requests to download results or to download a researcher's own Data should be sent directly to the DTU. All other requests for Data downloads must be sent to the SDC to refer to the wider Management Board / DLB for approval.

If, following approval from the Management Board / DLB it is necessary for Data to be downloaded from Computerome to a local server of a DIRECT Consortium member then a Data Transfer and Processing Agreement between the Data Controller (DTU) and the local processing center must be completed.

Responsibility for maintaining security of the Individual Level Data stored on the DIRECT Database rests with DTU.

A record of Data uploaded onto the DIRECT Database, requests for access to Computerome, and release of Data from Computerome will be collected and maintained by DTU. An updated table summarising all access requests by DIRECT consortium members and the purpose for the request will be made available to the SDC and the Management Board / DLB by the Database Manager.

Reminder: All individuals wishing to access and use data from the DIRECT Database must read and sign the DIRECT Data Access SOP, adhere to its terms and conditions and provide a signed copy of the last page of the SOP to the SDC before access is granted for the first time.

8. Data access principles and GDPR

8.1 Basic Requirements

In all instances where Data is accessed, the DIRECT consortium members agree to the principles below:

- This policy applies to Data transferred, used or generated by any DIRECT consortium members and/or affiliated entities;
- The person who transfers or receives Data is responsible for ensuring that his or her research team and/or affiliated entities comply with these principles;
- All Data can only be made available according to the terms and conditions outlined in the Data Submission Form, Data Transfer Agreement or the Data Access SOP;
- Should any conflict between the terms of the Project Agreement or DIRECT Legacy Agreement (DLA) and a DAF arise, the terms of the DIRECT Legacy Agreement will take precedence.
- The need to limit, protect and secure personal data under the General Data Protection Regulation (GDPR) 2018.

The Data can only be accessed by DIRECT consortium members if the following have been complied with:

- Professional conduct and Data protection requirements (GDPR) have been fulfilled for all Data accessed and shared.
- The intended use complies with the informed consent given by the relevant Donors.
- The intended use is in conformity with the Description of Work, Annex 1 of the Grant Agreement, and the provisions of the DIRECT Legacy Agreement.
- A Data Access Form (DAF), including an Analysis Plan which has been approved by the Management Board / DLB, has been completed and processed by the SDC.
- Each researcher/analyst requiring access to Data on Computerome has sent a signed copy of the Data Access SOP to the SDC confirming that they have read and will abide by the Terms and Conditions of data access.
- The Data will not be transferred or made available to any individual other than those under the supervision and control of the DIRECT project partners, their Affiliated Entities or Sub-contractors.
- The type of use outlined in the associated Analysis Plan / DAF has been approved by the DIRECT Management Board / DLB through the SDC.

- Researchers using Data obtained from the DIRECT Database will not retain Data in whole or in part beyond the use outlined in the associated Analysis Plan / DAF, unless this can be justified and such justification is provided in writing to the DIRECT Legacy Board;
- **Researchers must not transfer data from the shared analysis team folder on Computerome to any other folder.**

8.2 Responsibilities

DIRECT consortium members shall agree to ensure that they and any employees that process the Data shall:

- Comply with all applicable Laws, including GDPR, and take reasonable steps to ensure the reliability of those of its employees and that such persons have sufficient skills and training in the handling of the Data and comply with the Laws;
- Process the Data to the extent, and in such manner as is necessary to deliver the objectives disclosed in the DAF.
- Have, maintain, and comply with the all relevant Data Security obligations. These measures shall be appropriate to the harm which might result from any unauthorised or unlawful use.
- Shall deposit results, and code used to generate the results, to a specified location on Computerome.
- Analysis should only be performed on data that has been requested using a data DAF, in accordance with the Analysis Plan provided. Researchers should note that on receiving access to the requested data within the confines of the Computerome, it is possible they may be granted access to a wider dataset than they specifically requested. Researchers are trusted to select and access only the data they have requested, in line with the research outlined in the Analysis Plan.

Access to the DIRECT Database via Computerome is limited to authorised DIRECT scientists who must:

- Maintain security of the DIRECT Database by not sharing their username and password with anyone and must take all reasonable precautions to ensure their username and password remain confidential.
- Promptly report any breaches of DIRECT Database security to the DTU and the DIRECT Management Board / DLB.
- Have signed an obligation of confidentiality in relation to the Data (this is usually signed as part of an employment contract) if appropriate in their country.
- Take precaution in preventing intrusion software from being present on the equipment used to access the DIRECT Data.

8.3 Conditions for Downloading data from Computerome

- Individual level data must not be downloaded from Computerome (except in exceptional, pre-approved circumstances – see section 7.0 above).
- The basic requirements (8.1) and responsibilities (8 .2) outlined above apply to all data downloaded from Computerome. Analysts must follow these requirements when handling data downloaded from Computerome.

- Data downloaded from Computerome must only be used in accordance with the permissions granted through the data access process
- Where the Management Board /DLB have given permission for data (including individual level data) to be downloaded to a local secure server for the purposes of defined, limited analyses a Data Transfer and Processing Agreement must first be signed between the Data Controller (DTU) and the Receiving consortium partner. Data downloaded from Computerome should not be shared with other members of the DIRECT consortium outside of Computerome.
- Analysts should be aware that details of all downloads will be tracked, recorded and be traceable.
- Appropriate measures must be taken to ensure that data are stored and used securely, and not transferred insecurely to other members of the consortium. Computerome is the primary secure channel through which data should be shared.
- Appropriate care and attention must be taken to ensure that data are not copied or shared beyond the consortium, unless included in approved publications, presentations or posters.

9.0 Accessing Data by External Parties

External parties who are not part of the DIRECT consortium may be permitted to access the data accumulated during the course of the project - but only once the IMI-funded portion of the project has been completed. In the first instance the external party should ideally explore with an existing Consortium partner whether a collaborative research effort is feasible or practical. If such a research route is feasible then the Consortium partner should lead the application process. However this is not pre-requisite for a successful application and third parties are welcome to approach the Consortium for access to DIRECT data by contacting DIRECTdataaccess@dundee.ac.uk

The procedure for seeking access to DIRECT data by third parties (i.e. non-consortium partner) to address a particular research question on diabetes or related condition is the same as for a partner within the Consortium (see Diagram below). A number of conditions must, however, be met:

- The application must be from a *bona fide* research group from a recognised institution with a proven track record of research into Diabetes and related conditions.

- All data analysis must be conducted within the Computerome. Downloading of data for external analysis will not normally be permitted. A charge may be levied to cover the costs of the IT services provided by DTU who operate the Computerome and host the DIRECT data.

- A detailed Analysis Plan must be submitted by the applicant(s) describing the research question(s) to be investigated, the identity of the analysts involved, the procedures to be used and the timeline by when the research is anticipated to be completed. An estimate of the computing power required is also desirable.

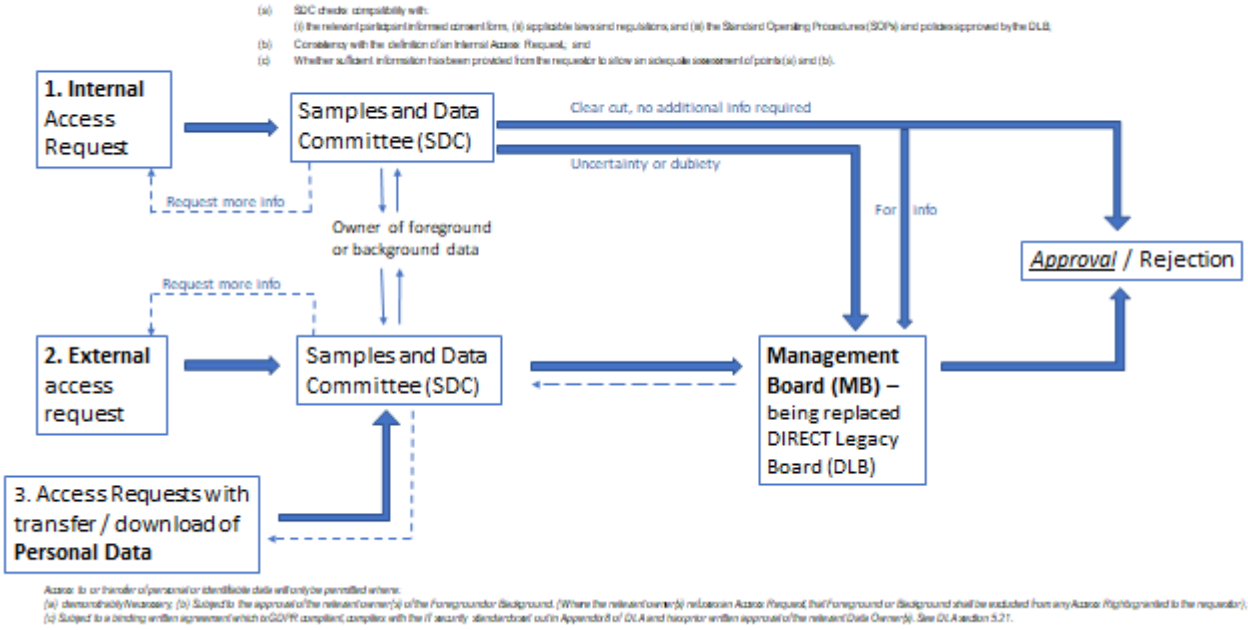
- The Analysis Plan and data access request must be reviewed and approved by the DIRECT Legacy Board who will ensure the planned analyses avoid duplication of effort and do not significantly overlap or impinge ongoing or planned data analyses within the consortium. The DLB will also consider whether the proposed research is consistent both with the broad aims and objectives of DIRECT and the Consent provided by DIRECT participants.

- The external applicant and its analysts will be subject to the same terms, conditions and requirements regarding data handling as a member of the DIRECT Consortium as outlined in the DIRECT Legacy Agreement. Specifically they must comply with the requirements of GDPR and in the event of any data breach or other significant event they must adhere to DIRECT policies and procedures for dealing with such instances.
- The external party must not sub-contract any data analysis function nor provide access to data or pass data on to any other party without the knowledge and permission of the DLB.

- Once completed, the results of the analyses must be deposited with the DIRECT consortium database and made accessible for others to use.

- Any publications arising from the analyses must acknowledge the DIRECT consortium.

Flow diagram for Review and Approval of Data Applications to the DIRECT Legacy consortium



10 Transfer of material within the DIRECT consortium.

Materials include any human tissue or other biological samples required for use in the Project.

Materials that could be shared as part of the DIRECT project include samples that have been brought to the project by DIRECT consortium members (Retrospective Samples), or samples that are collected through the DIRECT project itself (Prospective Samples).

Transfer of materials therefore includes the sharing of Retrospective Samples between project partners, or relocation of prospective samples to and from the central laboratory (UNEXE/UEFK). *In all cases informed Consent must have been provided and documented that permits use of the samples for the purpose(s) for which they are to be used*

10.1 Transfer of Retrospective Samples

In order to transfer Retrospective samples, a Materials Transfer Agreement (MTA) must be completed and co-signed by the sample custodian and the sample requestor. A copy of the counter-signed MTA is sent to the Programme Manager and WP9. The MTA includes information about how samples should be shipped, and states whether the sample can be shipped onward to another DIRECT consortium member following the initial transfer.

10.2 Onward shipment

In order for a sample to be shipped onward from the new custodian to another research group, the requester must check that the original MTA allows for this, and then fill in the relevant sections of the DAF, outlining the intended Analysis Plan for the samples. This form, along with the third page of the original MTA, is submitted to the SDC who will consider all requests for onward shipment, to keep oversight of the amount of each sample that is available, prioritising analysis if necessary. The SDC will encourage collaboration where appropriate.

10.3 Prospective Samples

An MTA is not required to deposit Prospective Samples in the central laboratories based at the University of Exeter. The Centers collecting samples will register these samples on the DIRECT Database, and the DIRECT Database will automatically keep track of which samples have been collected, and where they are stored. The database enables researchers to ship samples to the central laboratory, and automatically informs the central laboratory that a shipment has been dispatched. Once the shipment arrives at the Central Laboratory it will be checked in, and the database will automatically inform the provider of this via the bar codes system, keeping a record of the exact location of each sample at all times. The project plan identifies certain centers that will conduct specific analyses, for example DNA samples will be sent from the central laboratory to Oxford for sequencing, with the transfer enabled via the database. All other samples will be stored in the biobank at the central laboratory.

In addition to adhering to the relevant data access principles as specified in section 8, materials can only be accessed by DIRECT consortium members if the following have been complied with:

- Access to retrospective samples can only be made available according to the terms and conditions outlined in the Consent provided by the donor and in line with the Material Transfer Agreement that has been signed by the partners involved in the transfer;
- Should any conflict between the terms of the Project Agreement or DLA and an MTA, the terms of the DLA will take precedent.
- All the required authorisations, to perform the experimental work, under all applicable laws and regulations, at the place of investigation, must have been obtained.
- The intended use complies with the informed consent given by the relevant Donors.
- The intended use is in conformity with the Description of Work, Annex 1 of the Grant Agreement, and the provisions of the DIRECT Legacy Agreement.
- To share samples, an MTA has been completed by the relevant parties, and a copy sent to the SDC as a record of the transfer;
- The materials collected for the DIRECT Project will only be used for the DIRECT Project, as outlined in the Project Agreement or DLA, and will not be analysed or modified except as necessary for the purpose of the Project.
- The materials will not be transferred or made available to any individual other than those under the supervision and control of the Receiving Participant, its Affiliated Entities or Sub-contractors.
- The materials are to be used with caution and prudence in any experimental work, since not all of the characteristics are necessarily known. The Receiving Participant using the material shall bear all risks to it and/or any others resulting, directly or indirectly, from its use, application, storage or disposal/destruction of the materials.
- Upon completion of the Project, or the expiry or termination of the Project Agreement or subsequent DIRECT Legacy Agreement, any unused materials will be either returned to the Providing Participant which made them available or disposed of/destroyed in accordance with all applicable laws and regulations.

11 Requesting and transferring samples out with the DIRECT Consortium

External parties may request access to samples collected during the DIRECT studies- but only once the IMI-funded portion of the project has been completed. All remaining samples from DIRECT studies are held within and under the custodianship of the Peninsula Research Bank at the NIHR Clinical Research Facility at Exeter (UK) where they have been stored since collection and centralisation. The samples are primarily blood, serum and plasma samples but there are also urine and stool samples. Following the completion of the primary programme of studies, in line with the information provided to participants - and the consent they provided, it is intended that controlled access to residual samples collected during the course of the studies will be made possible for the wider diabetes research community as well as continuing for existing partners in DIRECT.

- Applications for access to any of the stored samples are made to the DLB who must sanction and approve any such application (making sure it falls within the scope of DIRECT, or diabetes and related conditions and meet the terms of the Consent provided by study participants). The SDC will triage requests on behalf of the DLB to ensure all the information and assurances required are provided.

- A Data and sample Access request Form (DAF) is available that seeks key information from

any requestor on the nature of the samples they require, why they are required and how they will be used. (see appendix). This should be accompanied by a detailed Analysis Plan.

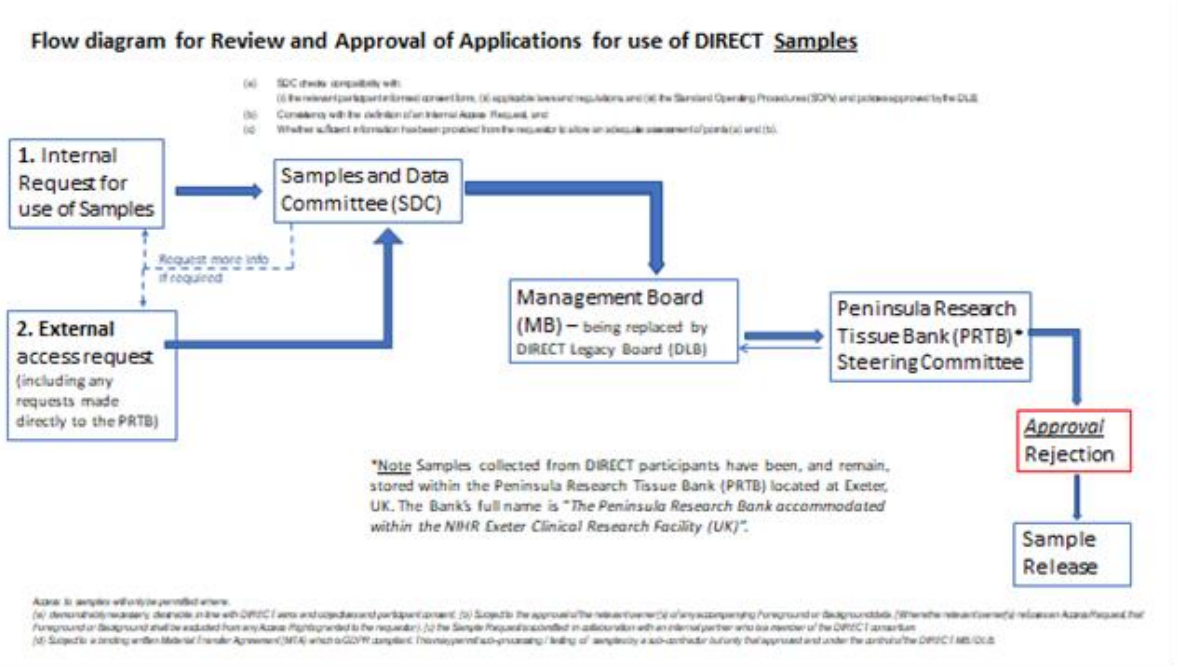
- The results of any testing conducted on DIRECT samples must be fed back into the DIRECT database so that the information can be shared and is made available to all (notwithstanding a suitable time period e.g. for publication).

- Costs for sample picking, shipping, analysis and return of residual sample will be met by the requestor.

- A Material Transfer Agreement (MTA) will need to be put in place between the Peninsual Research Bank, Exter and the recipient of the samples.

- In no circumstances should DIRECT samples be used to set-up a new biobank. The samples must only be used for the purposes for which they are relased and and any unused smaples must be returned.

A flow diagram for sample request is as shown below.



12 Summary of Revisions - Changes from previous version of this Policy

- Include provision for download of raw data from Computerome to local secure server in exceptional circumstances.
- Removal of references to Data Access Committee (DAC) and Data Extraction Team (DET) and replacement by the Samples and Data Committee (SDC) that acts on behalf of, and under the authority of, the DIRECT Legacy Board.
- Update document in light of the introduction of the GDPR and the planned DIRECT Legacy Agreement to take effect on termination of the Project Agreement
- Provision of ability for external parties to apply for, and be provided with, authorised access to DIRECT data and samples
- Revise numbering and other minor edits

13 Abbreviations

DAF: Data and sample Access Form

DIRECT: DIabetes REsearCh on patient straTification

DLA: DIRECT Legacy Agreement

DLB: DIRECT Legacy Board

DNA: Deoxyribonucleic Acid

DSF: Data Submission Form

DTA: Data Transfer Agreement

DTU: Technical University of Denmark

eCRF: electronic case report form

GDPR: General Data Protection Regulations

MTA: Material Transfer Agreement

SDC: Sample and Data Committee

SMS: Short Message Service

SSL: Secure Sockets Layer

SOP: Standard Operating Procedure

14. DEFINITIONS:

Affiliated Entities: means any legal entity listed in Appendix 8 to the Project Agreement that is under the direct or indirect control of a Participant, under the same direct or indirect control as a Participant, or is directly or indirectly controlling a Participant, control taking any of the following forms: (a) the direct or indirect holding of more than 50% of the nominal value of the issued share capital in the legal entity concerned, or of a majority of the voting rights of the shareholders or associates of that entity; (b) the direct or indirect holding, in fact or in law, of decision-making powers in the legal entity concerned;

Background: means information, including data and know-how which is held by a Participant prior to, on or after the accession to the Grant Agreement, as well as copyrights or other intellectual and industrial property rights pertaining to such information, and which is Necessary for carrying out the Project and which is defined in Appendix 3 to this Project Agreement;

Central Laboratory: University of Exeter
Consortium Member: means a party to the Project Agreement and "Consortium members" shall be interpreted accordingly.

Custodian: the person responsible for a sample being used in the DIRECT project.

Data: Summary Level Data and Individual Level Data together. Data may constitute the Background, or Foreground of a Participant.

Data Access: access to Foreground and Background Data.

Data Entry Clients: Computer used for Data entry.

Data Extraction Team: Individuals who have expertise in handling data and who help analysis teams determine which data are required to fulfil their Analysis Plans, and then to extract the required data from the database.

Data Provider: The participant or group which submits the Data to the database or provides the Data in transfers that are considered outside the scope of DIRECT and are determined by the associated Data Transfer Agreement.

Data Receiver: The participant or group which accesses Data on Computerome, or receives Data as a database download or through the transfer of Data for research outside the scope of DIRECT as determined by the associated Data Transfer Agreement.

Data Security Obligations: technical and organisational processes and procedures that will protect the Data against unauthorised or unlawful processing and accidental loss, theft, use, disclosure, destruction and/or damage which include:

(a) technical security measures;
(b) treating and safeguarding the Data as strictly private and confidential;
(c) minimising the disclosure of Data to third parties to the fullest extent possible;
(d) allowing access to the Individual Level Data strictly on a "need to know" basis employing appropriate access controls at all times;
(e) copying, reproducing and/or distributing the Data only to the extent necessary to perform the research as outlined in the Grant Agreement
(f) maintaining adequate back-ups for the Data to enable the Data to be recovered in the event of damage or loss.

Data Transfer: up- and/or down-loading of Data to and/or from the Database.

Data Transfer Agreement: an agreement generated by Data owner(s) and receiver for the transfer of Data from Computerome .

Computerome: A secure server hosted by the DTU that will be used for Data analysis in the DIRECT project.

DIRECT Authorised Personnel: People working in the DIRECT project who have been authorised to have access to the DIRECT database.

DIRECT Database: central DIRECT Database hosted and administrated by the Technical University of Denmark (DTU).

DIRECT Legacy Board: The successor to the DIRECT Management Board with responsibility for supervision and oversight of all DIRECT activities following the end of formal funding by IMI. It consists of a representative from each of the Partners remaining in the consortium

DIRECT Management Board: means a body comprised of the Coordinator, the Managing entity of the IMI JU funding, and the Work Package Leaders and responsible for the day-to-day management of the Project. Succeeded by the DIRECT Legacy Board

DIRECT Partner: a legal entity being a party of the *consortium*, contributing to the *project* and having rights and obligations with regard to the *IMI JU* under the terms of the *grant agreement.*

Donor: each patient or other donor of samples and/or Data.

Foreground: means the results, including data, know-how and information, whether or not they can be protected, which are generated under the Project and within the Project Objectives, and excluding Sideground. Such results include rights related to copyright; design rights; patent rights; or similar forms of protection.

Individual Level Data: Data attached to a single Donor that is directly identified as belonging to a single individual.

Laws: all applicable laws (including but not limited to Data protection laws and privacy laws) in any of the territories in the European Economic Area and Switzerland for the time being.

Material Transfer Agreement: the agreement co-signed by the providing participant and the receiving participant which allows the transfer of material for use in DIRECT.

Project: means the research activities carried out by the Participants as defined in Annex I of the Grant Agreement.

Project Agreement: means the Agreement for DIRECT and all of its appendices, together with amendments validly agreed in writing amongst the Participants.

Prospective Samples: samples that are collected through the DIRECT project itself.

Retrospective Samples: samples that have been brought to the project by DIRECT Participants.

Sideground: means the results, including data, know-how and information, whether or not they can be protected, which are generated by a Participant under the Project but outside of the Project Objectives and which are not needed for undertaking and completing the Project or the research use of Foreground. Sideground specifically excludes Foreground.

Sub-contractor: means a Third Party which has entered into an agreement on business conditions with one or more Participants, in order to carry out part of the work of the Project without the direct supervision of the Participant and without a relationship of subordination.

Summary Level Data: Data generated for a group of individuals with no means of inferring specific Data for any one individual.

User Interface: The means by which the user and a computer system interact, in particular the use of input devices and software.

15. Annexes

I. Data Submission Form
II. Data Submission SOP
III. Data and sample Access request Form (DAF)
IV. Data Access SOP
V. MTA SOP