CONSIDERATIONS FOR STUDY DESIGNS USING U-CAN MATERIAL

The U-CAN cohort enables users to address various types of questions across many disciplines of cancer research. Since patient material is precious, the U-CAN program board wants to raise awareness about the importance of well-planned study designs in order to conduct relevant research at the best possible practice. Hence, each study proposal including use U-CAN of material should carefully evaluate and motivate several aspects of the project plan. For instance, clearly define the study objectives, identify the need for chosen analysis methods, define necessary clinical data, describe the statistical methods, as well as consider the overall strengths and potential shortcomings of the study. When preparing a proposal, researchers are encouraged to contact U-CAN at an early stage in order to receive professional consultation regarding e.g. power calculations, statistical methods, data availability, etc. by emailing: u-can@igp.uu.se

The checklist provided on pages 2-3 is for researchers planning their study and for reviewers of the research proposal. By using the checklist researchers and reviewers can cooperate to improve the study and minimize the risk of overlooking preventable pitfalls.

General points to consider:

- Study objective. A study objective or hypothesis should be well-defined and based on available knowledge to address a relevant problem or question. Ideally, the objective is not open-ended, but specific in its goal and intention regarding the research question. A clear objective improves all other aspects of the study design.

- Statistical power refers to the probability of demonstrating the putative effect within the experimental design. The researcher should determine which sample size is minimally required for successfully demonstrating the effect within a certain confidence interval. A well-defined cohort size will minimize unnecessary overuse of scarce U-CAN material.

- Confounding factors are known or unknown factors that would influence the result and/or their interpretation. These include e.g. samples handling or other possible batch effects that could cause unknown variations in the observed results. In terms of clinical data, it needs to be investigated if there are underlying disease- or patient-related parameters that could affect the observed result, rather than the measured parameter being causative. Potential confounding factors should be described, identified, considered in the design and, if possible, corrected for.

- Inclusion/Exclusion criteria. When considering inclusion/exclusion there is a risk that the selected study set may be either limited or too general to allow for meaningful interpretations of the data. If the selection is too stringent there is a risk of introducing selection biases, and if it is too broad it may dilute the relevant variables for the intended study. This consideration relates to statistical power and the study objective. The inclusion and exclusion criteria should therefore be carefully considered in the study objective in terms of relevance and/or risk of bias.

- Controls. Using clinically relevant control samples/groups for comparison with experimental samples/groups is often required for interpretation of data. Choosing appropriate control subjects is therefore very important as the data derived from these controls will affect the outcome and translatability of the results. How relevant control subjects are defined for a particular study should therefore be addressed in the application.

- ■ *Black box items are to be considered by the applying researcher.*
- ○ *Blue circle items are to be considered by the reviewers of the proposal.*

Rationale and hypothesis

- ■ What is the purpose, goal and/or expected outcome of the study?
- ■ Could the results be interesting and/or publishable regardless of achieving a "negative" result?
- ○ Does the background description justify the study?
- ○ Does the study have clear and well-defined objectives?
- ○ Is the hypothesis reasonable?

Prerequisites

- ○ Is the study conducted in line with the ethical approval and the patient's informed consent?
- ○ Are necessary documents regarding e.g. MTA, confidentiality, data transfer, IP-rights, etc. in order?
- ○ Is the time plan reasonable?

Feasibility and collaboration

- ■ Does the research group have prior experience of this type of study?
- ■ Is there potential to follow-up on the findings in other studies (e.g. addition of new cases or follow-up on outcome)?
- ○ Would there be benefits of joint collaboration with ongoing projects involving similar material?
- ○ Does the collaborative network possess the necessary competence to reach the objectives?
- ○ Could additional researchers or clinicians strengthen the collaborative network?

Statistics and confounders

- ■ What is the statistical power overall and/or for investigated subgroups?
- ■ Which statistical methods will be used?
- ■ Is specific statistical competence available in the group?
- ■ What is known about parameters that could and/or will influence the results:
  - ▪ Sample factors (e.g. arm to freezer time, storage conditions, temperature changes, sample homogenization, purification methods)?
  - ▪ Clinically related factors (e.g. tumor stage and grade, histology, treatment, clinical lab results, radiology, WHO-status, etc.)?
  - ▪ Patient-related factors (e.g. age, gender, BMI, lifestyle, heredity)?
- ○ Are the power calculations and the intended statistical methods reasonable?
- ○ Has the research group overlooked potential confounders?

Samples

- ■ Which are the inclusion and exclusion criteria for patients?
- ■ Is there a risk for introducing selection biases?
- ■ What will be used as control samples and how are these controls appropriate for the study objective?
- ■ What is the required sample amount/volume?
- ■ Will the entire volume be needed and used for the described analyses?
- ○ Is the design suitable for use with U-CAN samples?
- ○ Would there be an added value of using longitudinal patient samples?
- ○ Are the requested samples especially valuable (e.g. limited supply)?
- ○ Will the requested amount of material impede possible future research projects?

Clinical data

- ■ What are the sources for clinical data?
- ■ Are the necessary clinical variables available in sufficient quantities?
- ■ How, where and by whom will clinical data be stored and handled? Will data be transferred or processed abroad?
- ■ Does the study require access to sensitive personal information such as personal numbers?
- ○ Could additional registries for data be used?

Analysis of samples, methods and research data

- How, where and by whom will the analysis be performed? Will samples be analyzed and/or processed abroad?
- How, where and by whom will the data from the analysis be stored and analyzed?
- Does the research group or collaborative network have experience in working with the analysis methods?
- Will the samples be used for method development purposes?
- Are the analysis methods optimized for the sample amount/volume needed?
- How will, or can, the study findings be validated in both technical and scientific terms?
- Are the analysis methods reasonable or are alternative/better methods available?
- Are the suggested validation methods and/or strategies reasonable?