TEMPLATE RESEARCH PROTOCOL

for non-WMO-applicable research

19-01-2023, versie 2

Full title of protocol	The COMFORT Study: determining the most comfortable radiotherapy matrass
Short title or Acronym	The COMFORT study
Protocol ID / Panama number	6553
Version	1.0
Date	30-03-2023
Coordinating investigator[1]/ Project leader	N.A. Hoffmans-Holtzer P.O. Box 2040 3000 CA Rotterdam The Netherlands Internal postal address: NF-533 Email n.hoffmans-holtzer@erasmusmc.nl
Principal investigator[2] **(in Dutch: hoofdonderzoeker/ uitvoerder)** **<Multicenter research[3]: principal investigator per site>**	S.F. Petit P.O. Box 2040 3000 CA Rotterdam The Netherlands Internal postal address: NF-529 Email s.petit@erasmusmc.nl
Sponsor[4] (in Dutch: verrichter/opdrachtgever)	Department of Radiotherapy, Erasmus MC Cancer Institute
Subsidizing party[5]	N/A

Name	**Signature**	**Date**
Head of Department: *Prof dr. Remi Nout*		3-4-2023
Principal Investigator: *Dr. ir. S.F. (Steven) Petit*		30-3-23

1. *Coordinating investigator: Investigator who bears the responsibility for the coordination of investigators operating in the various centers participating in multicenter research. Not all multicenter research will have a coordinating investigator. There is no requirement to appoint one. A project leader has the responsibility to develop a research protocol and to complete the study within the predefined goals.*
2. *Principal investigator: Investigator who has the overall responsibility to comply and to complete the study within the predefined goals.*
3. *Multicenter research: as an alternative you can also state that these are specified in the list with participating centers including principal investigator. This separate document with version date must be uploaded under category I1.*
4. *Sponsor: The party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or the investigator's employee. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.*
5. *Subsidizing party: A party that provides funding for a study but does not commission it*

Table of Contents

Please note that it is not allowed to remove paragraphs from this template protocol. If a paragraph is not applicable, please mention this in the specific paragraph, preferably with a short motivation.

List of abbreviations and relevant definitions*

CTA	Clinical Trial Agreement
De novo biobank	A new data, human material or imaging collection
DMP	Data Management Plan
DPIA	Data Protection Impact Assessment
DTA	Data Transfer Agreement
Exception consent	Form Care for data Template, in Dutch: Formulier uitzondering toestemming
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation in Dutch: Algemene Verordening Gegevensbescherming
IC	Informed Consent
IFU	Instruction For Use
MTA	Material Transfer Agreement
NWTC	Non-WMO Review Committee; in Dutch: Niet WMO Toetsingscommissie
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet Algemene Verordening Gegevensbescherming
WMO	Medical Research Involving Human Subjects Act, in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

**Please add any new definitions that are used in the research protocol*

Summary

The summary should give a brief description of the central question that the research is intended to answer and its justification. It should specify the hypothesis (if applicable) and the research objectives. In addition, the synopsis should briefly describe the design, population, methods and procedures of the study. Finally, if applicable, the nature and extent of the burden and risks should be indicated.

Rationale
Please specify background and hypothesis (if applicable) of the study.

The Erasmus MC radiotherapy department treats approximately 5500 patients per year. Roughly 2000 patients are treated with palliative intent, which means that these are patients with metastasized cancer, who need to be irradiated to relieve complaints and/or improve their quality of life of their final stage of life. A large portion of the patients are treated for painful bone metastases at the dedicated outpatient clinic at the Erasmus MC radiotherapy department.

The current radiotherapy workflow consists of a treatment preparation and a treatment delivery phase. At the dedicated outpatient clinic, patients are treated at the same day they had their intake or, if patients prefer, the day after. This means that the regular preparation phase of multiple days (up to a week) is reduced to less than a day (typically 3 to 6 hours in total). During the preparation phase a CT scan of a patient is acquired. This CT-scan is used to delineate the target volume and the organs at risk. Based on this information a patient specific treatment plan is generated. During the treatment delivery phase (approx. 15 minutes) it is very important that the patient is positioned according to the CT-scan. Therefore patients are positioned on an uncomfortable hard flat table top during both treatment phases. To somewhat improve the comfort for this patient group a thin mattress (not labeled as a medical device) is added during the normal clinical routine.

To increase comfort and relieve the pain during the CT-scan and treatment delivery a thicker mattress was developed together with Royal Health Foam, and 6 samples were produced. These mattresses are no medical devices, since any effect they may have on the treatment is negligible. No special guidelines are available for these kind of mattresses. All mattresses were approved for standard clinical practice by the responsible medical physicist using the appropriate procedures at the department of radiotherapy. These procedures included radiation transmission measurements, ease of use and cleaning and phantom measurements to quantify the sag of the mattresses.

Objective(s)
Please specify the main and secondary objectives of the study.

The primary objective is to determine if patients find the (newly developed) thicker radiotherapy mattress more comfortable than the standard thin matrass.

The secondary objectives are:

1. To determine if patients who experience pain while lying on any of the matrasses find the thicker radiotherapy matrass more comfortable than the standard thin matrass.
2. To determine if the patient experience less pain while lying on the thick matrass compared to while lying on the thin matrass
3. To record patient motion during treatment using the optical surface monitoring which is already used in routine clinical practice

Study type
Please describe the design of the study.

A prospective observational study

Study population
Please describe the study population, e.g., healthy volunteers, xx year old.

Only patients (age ≥ 16) with bone metastasis in thoracic, abdominal and pelvis region who are treated at the one-stop shop for palliative radiotherapy are included in this study. The total number of patients that will be included is 45. See section 4.5 for more details.

Methods
Please describe how you conduct research and which methods are used.

The study will be discussed with the patient by the treating physician during intake, or right after by a radiotherapy technologists (RTT). For patients that sign the informed consent, prior to planning-CT acquisition, patients will be asked to lie on each mattresses for 1 minute. Next patients are asked to score the pain they experienced, on a scale of 0-10 while lying on each mattress. Also patients are asked which mattress they prefer. Next the CT scan is acquired of the patients lying on the mattress of choice. The same mattress will also be used during irradiation. Note that both mattresses have been released for clinical use, and the choice of mattress does not affect the quality of the treatment. Only potentially the experienced comfort.

Right before start of treatment and in line with clinical practice, patients will be positioned on the treatment couch with the aid of the optical surface monitoring system. The optical surface monitoring system makes a 3D scan of the surface of the patient from which it calculates the motion (3 translations, 3 rotations) of a predefined region of interest. During treatment, the quality of the treatment is evaluated based on the motion information, and if necessary, RTTs could pause the delivery. Specifically for the study, the motion of the patient will be assessed in more detail after treatment.

Burden and risks
Please describe the burden and risks associated with participation.

There is no additional risk introduced by the treatment on thick mattress.

The burden of the patient is limited to testing the mattress prior to CT-acquisition and scoring of its comfort. Which takes about 5 minutes. Both mattress are suitable for the radiotherapy treatment. So the choice of mattress does not affect the treatment.

Recruitment and consent
Please describe the recruitment and informed consent procedures.

Patients will be asked to sign informed consent by the radiation oncologist during intake or by the RTT right after intake.

1. Introduction and rationale

Please specify background and hypothesis (if applicable) of the study.

Together with Royal Health Foam, the department of Radiotherapy developed a new mattress, which could replace the thin mattresses that are currently in use for patient positioning during treatment. The only purpose for this mattress is to offer comfort to patients, that are treated on a flat treatment couch at the radiotherapy treatment machine. To improve the comfort of the mattress, the new mattress is thicker than the mattress currently in use. Especially for patients that are treated with palliative intent who are often frail and in pain, it is expected that the thick mattress could provide a more comfortable treatment experience.

Because the thick mattress should not interfere with the dose delivered by the treatment machine, the thick mattress is made of dedicated materials. Although the thick mattress is not considered a medical device, all samples were evaluated for safe use in the clinic in terms of radiation transmission, and ease of use and cleaning. Also the positioning stability of a phantom and two volunteers on the mattress was assessed and within tolerances. After which the mattress has been approved for clinical use at the department of radiotherapy.

2. Objective(s)

The objectives of the study are the questions that the study is intended to answer and are based on the scientific rationale and/or hypothesis formulated.
Please specify the main and <if applicable> secondary objective(s) of the study.

The primary objective is to determine if patients find the thicker radiotherapy mattress more comfortable than the standard thin matrass.

The secondary objectives are

1. To determine if patients who experience pain while lying on any of the matrasses find the thicker radiotherapy matrass more comfortable than the standard thin matrass.
2. To determine if the patient experience less pain while lying on the thick matrass compared to while lying on the thin matrass
3. To record patient motion during treatment using the optical surface monitoring device that is used in routine clinical practice for patient positioning.

3. Study type

3.1. **Study type**

☐ Retrospective
☒ Prospective
☐ Combination Retrospective/Prospective

3.2. **Single center / Multicenter**

☒ Single center
☐ Multicenter

3.3 **Check all the applicable boxes**

☒ Medical records (re-use of data from healthcare, including AI)
☐ Case report
☐ Re-use data from research
☐ Evaluations of quality of healthcare (retrospective)
☐ Research with additional use of residual material from regular healthcare
☐ Research with re-use of human material from research or existing biobank
☐ De novo biobank
☐ Phase IV research
☒ Healthcare evaluation research (prospective)
☐ Research with medical devices
☐ Research with In Vitro Diagnostic Tests
☐ Other research, describe

4. Study population

4.1. Study population

☒ Adults (16 years and older)

☐ Minors (younger than 16 years)

☐ Incapacitated adults (16 years and older)

☐ Incapacitated minors (younger than 16 years)

4.2. Population (base)

Describe the population (patients and controls if applicable), e.g. healthy human volunteers, xx-xx year old, adults, minors and/or incapacitated adults or minors. Specify and justify the number of subjects required for the study.

Patients that are treated at the one-stop shop at Erasmus MC for palliative radiotherapy. For the required number of patients see section 4.5

4.3. Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age: ≥ 16
- Patients treated for bone metastasis in thoracic, abdominal and pelvic region
- Patients have read, understood and signed the informed consent of the COMFORT study.

4.4. Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients not willing or able to test two mattresses (regular and thicker)

4.5. Sample size calculation

Specify and justify the number of subjects required for the study, estimated number of subjects, or number of subjects in the period of evaluation.

The estimated number of patients needed for evaluation of mattress preference is 36. This number is calculated for a one-sample proportions z-test with an estimated preference for thick mattress of 70%, with ±15% error margin and a confidence level of 95%. These power calculations were performed by Yvette van Norden, statistician at Erasmus MC.

For some patients the optical surface monitoring system may not be able to accurately detect the body of the patients, for instance due to too much body hair. These patients will be included for the primary objective, but cannot be evaluated for the third secondary objective. To account for these patients, accrual will continue until either 36 patients are included that can be evaluated for all objectives or a maximum number of total patients of 45.

5. Methods

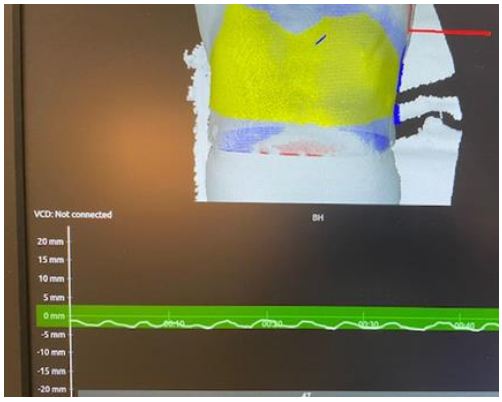
5.1. Research methods

Please describe how you conduct research and which methods are used, e.g., questionnaires, human material collection, extraction of data from medical records, analysis of images, the use of an app/medical device/diagnostic test, clinical tests to be performed, etc. Include information

on frequency, duration, volumes. If a Data Management Plan is available, please upload DMP.

Included patients are asked to test the regular and thick mattress for 1 minute each, right before CT scanning. Directly after testing each mattress, patients are asked to score whether they experienced pain lying on any of the mattress (score 0-10) and asked which mattress they prefer. Next the CT scan will be acquired with the mattress of choice. Note that the choice of mattress does not affect the quality of the treatment.

In line with clinical routine, right before treatment, the positioning of the patient on the treatment couch is assessed using an optical surface scanning system. The system acquires a 3D scan of the surface of the patient to verify the patient position right before treatment. To evaluate the quality of the treatment, the patient potion during treatment is also monitored by the same system. Of the 3D surfaces scans that are acquired over time during treatment, only the 3D motion (3 translation and 3 rotations) will be assessed. In the figure below the 3D surface is indicated in white, with the predefined region of interest in yellow. The average motion is shown as the white curve within the green rectangle. All data is stored as radiotherapy treatment information in the context of the treatment. For the research, however, only the 3D motion will be assessed. Next the motion vector will be post-processed using a fast Fourier transform to filter out the breathing motion.



5.2. **Standard clinical care versus extra for research**
Indicate which of the methods are part of standard clinical care and which tests and/or visits are extra for research purposes i.e., not standard clinical care.

The testing and scoring of both mattresses is extra for research purposes, i.e.: not standard clinical care. The monitoring of the patient positioning stability will be applied conform standard clinical care.

5.3. **Burden and risks**
Please describe the burden and risks associated with participation, e.g. the amount and number of blood samples, biopsies, liquor, hair, urine, nails, saliva etc., the number of site visits, physical examinations or other tests, questionnaires or diaries that have to be filled out, physical and psychological discomfort associated with participation.
If there is no burden and risk because there is no direct involvement from participants needed please describe this.
If a study is carried out with minors or incapacitated subjects, it should also be specified whether the risks are negligible and the burden minimal and why the study is group related (i.e., study can only be done using these patients groups).

There is no additional risk introduced by the treatment on a thicker mattress.

The only additional burden of patients in the trial is the additional question asked to score the comfort of both mattresses prior to CT-acquisition, which is considered to be negligible.

5.4. **Medical device(s) / In vitro diagnostic tests**
Describe which medical device and/or in vitro diagnostic test is used, what the intended use of the medical device is and whether the medical device/diagnostic test is already available in the participating centers.

Both mattresses are not considered to be a medical device. They are not part of the treatment machine, can be safely omitted and their impact on the dose delivery is negligible.

Note here that this study is similar to the example about randomized studies at the CCMO website (https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/your-research-is-it-subject-to-the-wmo-or-not). This example describes a study on the prevention of decubitus, where subjects are randomized to the use of mattress A or B in their bed. Within the context of the WMO no rule of conduct is imposed in this example, and the use of another mattress is not considered as an infringement of the physical and/or psychological integrity of the subject. The website concludes that such randomized studies are not subject to the WMO, providing that no other procedures or rules of behavior are imposed (for instance taking blood samples). Note that he current study does not even randomize.

6. Incidental findings

6.1. **Chance of incidental findings**
Is there a chance of incidental findings?

☐ Yes
☒ No

6.2. **Procedures**
If yes, describe who will be notified and how the subjects and other parties will be notified in case of incidental findings from the study that may be in the interest for the participant's health.

Not applicable.

7. Statistical analysis
Describe how data will be analyzed

7.1 **Main study parameters/endpoints**
Please describe the main study parameters/endpoints.

- The percentage of patients that preferred the thick mattress

7.2 **Secondary study parameters/endpoints**
Please describe the secondary parameters/endpoints, how the analysis will be done for the outcome parameters.

1. Average comfort experienced by patients (score: 0-10) while lying on the thin and thicker mattress.

2. Average pain experienced by patients (score: 0-10) while lying on the thin and thicker mattress.
3. Patient motion

7.3 Other study parameters

Please describe the other parameters/endpoints.

- Treatment site
- Weight

7.4 Analysis

Please describe how the analysis will be done for the outcome parameters.

- The mattress preference is calculated as the fraction of patients that preferred the thick mattress: number of patients who chose the thick mattress / the total number of patients included. Also the confidence intervals will be investigated.
- The experienced comfort per mattress is calculated as the average of the patients' scores. Also the distribution of the scores per group (preference for thin vs thick mattress) and confidence intervals will be investigated
- The experienced pain per mattress is calculated as the average of the patients' pain scores. Also the distribution of the scores per group (preference for thin vs thick mattress) and confidence intervals will be investigated
- The motion is defined by the translation (in 3D) measured by the AlignRT® camera system, after exclusion from the breathing motion based on a fast Fourier transform.

8. Ethical considerations

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version, date, see for the most recent version: www.wma.net), Gedragscode Gezondheidsonderzoek 2022 and in accordance with other guidelines, regulations and Acts (if applicable, please specify).

8.2 Informed consent

Will the subjects be asked for informed consent?

☒ Yes *(Upload Participant Information Letter and Informed Consent)*

☐ No, consent already given in previous study *(Upload Participant Information Letter and Informed Consent previous study)*

☐ No, this research will be performed under the exception consent *(Upload form Care for data Template, in Dutch: Formulier uitzondering toestemming)*

☐ Other (e.g. partly, indirectly) *Please describe the situation.*

8.3 Recruitment and informed consent procedures

If yes, please give a description of the recruitment and informed consent procedures. How and by whom (investigator, supervising doctor, other person) participants will be informed about the study and asked for their consent, how much time will they be given to consider the decision. The patient information letter with informed consent form should be attached as a separate

document.

The COMFORT study will be explained to eligible patients by the radiation oncologist during intake or by the RTT right after intake. After explanation, patients will be asked to sign informed consent.

Please note that for patients treated at the One-Stop Shop for palliative radiotherapy, time between first consult and CT-scan acquisition is limited, and therefore the time to consider participation is relatively short (1 to 60 minutes). However, considering the limited burden for the patient and the simplicity of the research question, this short time should be sufficient.

8.4 **Exception consent**

If no, exception consent: *describe how it is safeguarded that subjects are excluded who have objected against the re-use of their data, human material, images.*
The Form Care for data Template should be attached as a separate document.

Patients can always withdraw from the COMFORT study by requesting their radiation oncologist.

9. Handling and storage of data / images / sound recordings / photos / film recordings

9.1 **Data / images / sound recordings / photos / film recordings**

Please describe which data / images / sound recordings / photos / film recordings is/are used, are they obtained for regular healthcare purposes or in the context a research project, or a combination.

- Age (healthcare purposes)
- Tumor site (healthcare purposes)
- Weight (healthcare + research purposes)
- Surface monitoring (3D motion signals only) (healthcare + research purposes)
- Pain scores (healthcare + research purposes)
- Comfort scores (research purposes)

9.2 **Privacy protection**

Describe how subject's privacy is protected. Describe how, when and by whom data is coded (unique code without initials or date of birth) and how the key table is safeguarded, mention the General Data Protection Regulation.

Please note: The handling of personal data has to comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming en Uitvoeringswet Algemene Verordening Gegevensbescherming).

At enrollment in the study, each patient will be assigned a unique study ID number. Only pseudo-anonymous data using this study ID number will be provided to investigators for analysis; a separate file with the identifying information will be kept at a separate location on a secured network directory of Erasmus MC with restricted access, i.e. only for persons directly involved in data collection and data validation, and to the Erasmus MC ethics committee or any

other person or agency required by law (e.g. for purposes of monitoring or research audits). All personal data will be processed in full compliance with the AVG and UAVG.

9.3 **Handling and storage of data**
Describe how data is handled and stored (i.e., which data management system/data capture system), anonymous / pseudonymized / coded / identifiable, who has access to the coded source data, how long data will be kept, which steps are taken to ensure data security, what happens with the data after the research has been completed.

All data will be handled conform the Dutch Act on Implementation of the General Data Protection Regulation (in Dutch*: Uitvoeringswet Algemene Verordening Gegevensbescherming (UAVG)*) and the Erasmus MC privacy regulations. Data will be collected in Castor EDC with controlled access rights and an automated audit trail. Data generated during the surface monitoring will be stored in an access controlled research environment on the servers of the department of Radiotherapy. The data will not contain directly identifying data. Instead a unique study ID number will be used. All data will be stored for 10 years after ending the study. Collected data will be secured against unauthorized access and will be stored and secured by the department of Radiotherapy. Only pseudo-anonymous data will be provided to investigators for analysis. The separate file with the identifying information will be kept at a separate location on a secured network directory at Erasmus MC.

9.4 **Handling and storage of images / sound recordings / photos / film recordings**
Describe how images / sound recordings / photos / film recordings are handled and stored, how the subject's privacy is protected, anonymous / pseudonymized / coded / identifiable, what happens with images after the research has been completed.

Data generated during the surface monitoring and imaging data (CT scans) will be pseudonymized by removing all identifying data and adding the unique study subject ID number. All details regarding pseudo-anonymization are described in the department protocol for image pseudo-anonymization which is also approved by the Erasmus MC PKO. The imaging data are stored on a secure server with controlled access for members of the project team only. Imaging data used for this research will be archived after the project has ended and kept for 10 years.

9.5 **Approval of access to data / images / sound recordings / photos / film recordings**
Describe how the access is approved. Is access granted by the Data Board, Department, Principal investigator of the collection or other?

The Department of Radiotherapy applies the same criteria for approval of requests to use imaging data for research as are applicable for use of data through the Health Data Platform. The Outcome Unit of the Dept. of Radiotherapy will perform a check on registration of the research project in PaNaMa and completion of the DPIA tasks, approval by the niet-wmo committee, availability of a data management plan, and a safe storage location for further processing of the data. After this check has been successfully completed the imaging data and surface monitoring data will be pseudonymized and transferred to the research environment.

10. Handling and storage of human material

10.1 **Human material**
Please describe which human material is used.

Not applicable

10.2 **Check all the boxes which are applicable to the human material origin:**

☐ Residual material from regular healthcare

☐ Research (material acquired from a previous study).
Add the reference of the study i.e., MEC-number Erasmus MC.

☐ Re-use of human material from existing biobank
Describe whether the human material originates from research into the same disease.

☐ Other, *please specify*

10.3 **Handling and storage of human material**

Not applicable

☐ Anonymous, i.e. the material can never be traced back to an individual subject

☐ Pseudonymized/Coded

☐ Identifiable

Describe how human material is handled and stored (i.e. which data management system / data capture system), anonymous / pseudonymized / coded / identifiable, who has access to the human material, how long the human material will be kept, what happens with the data after the research has been completed.

Not applicable

Biobank
In case of new human material collection (biobank), describe how the human material is coded and stored (which registration system, Central Biobank or other location), who has access to the registration system and human material, by whom the key to the code is safeguarded, how long and where human material will be kept, what happens to the human material when the storage period is expired.

Not applicable

Approval of access to human material
Describe how the access is approved. Is access granted by the Department, Principal investigator of the collection or other?

Not applicable

11. Exchange, sharing or transfer of data and/or human material and/or images

Describe with which organization the data and/or human material and/or images are shared, are they profit or non-profit organizations, whether these organizations are in the EU or outside the EU, how the privacy of subjects is protected outside the Erasmus MC and describe the procedures regarding the exchange(s), whether a Data Transfer Agreement/Material Transfer Agreement is available (if

yes, please upload the DTA/MTA).

Collected data will not be exchanged, shared or transferred outside the Erasmus MC.

12. Amendments

Amendments are changes made to the research after a favorable opinion by the NWTC has been given.

All amendments must be submitted to the NWTC that gave the favorable opinion.
Substantial amendments must be approved by the Niet WMO Toetsingscommissie before they can be implemented.

13. End of study report

Within one year after the end of the study a final study report will be submitted with the results of the study, including any publications/abstracts of the study.

In case the final study report will not be available within one year, another term should be defined including the reasons.

14. Publication

Do you have the intention to submit the study results in a manuscript for publication in a journal:

☒ Yes

☐ No, *please motivate*

Describe when the final study report with the results of the study will be submitted.

The final report is expected to be submitted Q2 2024

15. References

Include a list of all key references published in peer review journals that are relevant for the study and are discussed in the protocol

To the best of our knowledge, no relevant literature exists with respect to mattress development for radiotherapy.

16. Attachments

☒ Participant information letter and Informed consent document

☐ Care for data Template – Formulier uitzondering toestemming

☒ Questionnaires

☐ Data Management Plan

☐ Data Transfer Agreement

☐ Material Transfer Agreement

☐ Clinical Trial (Site) Agreement

☐ Other, *please describe*