Gravity of Flow

The FlowSure clinical validation study protocol

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PROTOCOL TITLE The clinical validation of the FlowSure automated urine production monitor'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor but referred to as a subsidising party.**
ADE	**Adverse Device Event**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Current manual diuresis monitoring is labour intensive, to optimally monitor hospitalised patients with a urine catheter. The automated FlowSure monitor aims to automate diuresis monitoring and data processing to the electronic medical record.

Objective: The primary endpoint is the *accuracy* of urine production monitoring using the automated FlowSure monitoring compared to the standard manual method of monitoring.

Study design: Part A is single arm intervention study in which patients will receive *both* the manual monitors and automated FlowSure monitor (both devices will be used in conjunction). Part B is a two-arm randomized non-blinded intervention study in which patients will be monitored with *either* the manual monitoring or automated FlowSure monitor.

Study population: Patients admitted to the hospital who - for medical reasons unrelated to the study have a urine catheter inserted.

Intervention (if applicable): in part A patient will undergo double urine monitoring as they receive both the manual urine monitor and automated FlowSure monitor.
In part B patients will be randomized to monitoring with the manual monitor or to automated monitoring with the automated FlowSure monitor.

Main study parameters/endpoints: The primary outcome event in Part A will be the *accuracy* of urine measurement over two set time intervals (a nursing shift of 8 hours and a full 24-hour period) using manual monitoring and automated monitoring.
The measurements of both the manual and the automated urinemonitor will compared against the golden standard: the total urine production measured in a measuring cup by draining the collection bag.
The primary outcome in part B of the study will accuracy of measurement over a set time interval (a nursing shift of 8 hours and a full 24-hour period) using manual monitoring *and* automated monitoring. Therefore, the completeness of the hourly diuresis registration will be compared between the manual and automated measurement groups.

Nature and extent of the burden and risks associated with participation, benefit, and group relatedness: There is no direct benefit for patients participating in the study. The societal/research benefit of the study lies in the potentially improved diuresis monitoring and registration in the medical record of the patient which will improve the quality, (costs) effectiveness and accuracy of patient monitoring and therefore patient safety.
Risks: The foreseeable added risks associated with the use of FlowSure in Part A are negligible as using the automated monitor will be additive to the manual measurements.
In part B the patient will be monitored with either a manual monitor or the automated FlowSure monitor. If either monitor fails, the hourly urine production can be estimated by dividing the total urine collection since monitoring started by the hours that have passed since insertion of the urine catheter.

Risk-benefit analysis: Since the expected clinical-scientific benefit of this study is estimated as large and the clinical investigation is, in the opinion of the investigators, proportional to the added risk associated with the use of the medical device, which is estimated as low, the overall risk-benefit profile of the study is favourable.

1. INTRODUCTION AND RATIONALE

Diuresis, the amount of hourly produced urine, is a vital parameter that is routinely measured in patients hospitalized patients. Up to half of the millions of patients hospitalized each year in nursing wards and all intensive care unit patients and those undergoing surgery have an indwelling urine catheter inserted into the bladder in order to continuously measure urine production. A reduced diuresis of for example less than 30 millilitres per hour is the first sign of hemodynamic and clinical instability of the patient that can be the result of a (occult) bleeding, infection, or heart failure.

The first response of the body to mitigate hemodynamic instability is to retain fluid by decreasing diuresis. The traditional monitors are insufficient as reading and registering diuresis manually every hour for every patient is burdensome for nurses and often deprioritized due to time constraints. Unlike most other vital parameters, diuresis cannot simply be measured instantly like heart rate or blood pressure but requires monitoring over time which complicates registration. Hourly diuresis registration often is incomplete as nurses are unable to register at set times: a nurse assisting one patient cannot register urine production at the same time of the other patients under his or her watch.

As a result, information about the vital parameter diuresis is often not available when the clinical situation of the patient deteriorates and therefore compromising the patient safety. With accurate and complete information regarding changes in diuresis that prompt automated alerts, a clinical deterioration of the patient’s condition will be detected earlier and intervened upon sooner, without an extra burden/time costing intervention of the nurse.

The automated FlowSure monitor is a digital hanging scale that continuously weighs urine production over time, as urine flows through the urine catheter into the catheter bag underneath the patient's bed. FlowSure visualizes the most recent hourly urine production on the screen of the medical device and transmits the generated data to the patient’s electronic medical record.
Since the specific weight of urine is equal to water and thus one gram is equal to one millilitre, the increase in weight of the urine bag over time is a surrogate for urine production.

The FlowSure does not come into contact with the patient or the patient's urine(bag), nor in contact with the nurses' hands for detection or view of the volume.
The urine flows from the bladder through the catheter into the catheter bag under the patient's bed, while the catheter bag is attached to the FlowSure.
Instead of attaching the urine bag to the bed, the urine bag is attached to the FlowSure so that the weight can be continuously measured and recorded.
Since FlowSure does not come into contact with the patient or the urine, it is *reusable* after surface disinfection of the medical device. The reusability will make the FlowSure cost effective to operate.

The FlowSure aims to achieve two goals:

1. Improving patient safety by providing complete registration of urine production with automated alerts
2. Reducing the workload for nurses by automating and directly registering urine production in the electronic medical record.

Figure 1: the traditional manual urine monitor.

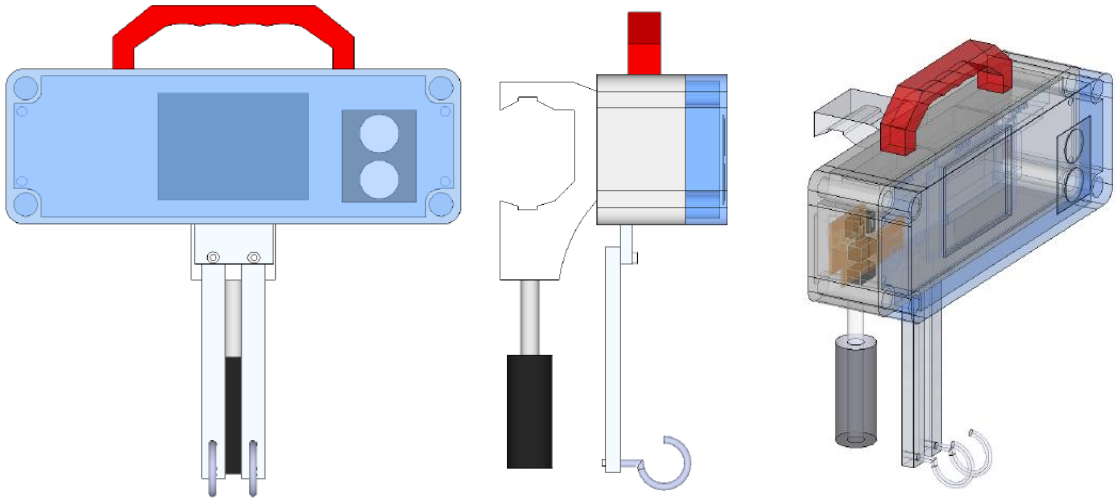


Figure 2: computer aided design of the intended demonstrator second generation FlowSure prototype

Preclinical research

The FlowSure team has conducted a non-human study at the cardiology department of the Amsterdam UMC. In the study we have demonstrated the functionality and accuracy of the device in a mock set-up. In the set-up a Braun infusion pump was used to simulate a patient with diuresis and the investigational FlowSure device was test for operability, accuracy, and safety. The results demonstrated that the measurement with FlowSure is more accurate than the Braun infusion pumps that are currently in use in our hospital. The infusion pump was set at a fixed rate of 50 millilitres per hour. The golden standard was the manual measurement with a measuring cup. The accuracy of the FlowSure was within 1% margin from the golden standard, whereas the margin for the infusion pump is up to 10%.

2. OBJECTIVES

The objective of the study is in part A of the study protocol to demonstrate that in clinical care the investigational FlowSure device is able to monitor urine production accurately and safely. The aim in part B of the study is to demonstrate that the use of the investigational FlowSure device will result in more complete and (cost effective) urine production registration.

3. STUDY DESIGN

The study will consist of two parts. Part A is single arm intervention study in which patients will receive both the manual monitors and automated FlowSure monitor (both devices will be used in conjunction). Part B is a two-arm randomized non-blinded intervention study in which patients will be monitored with either the manual monitoring or automated FlowSure monitoring.
In both part A and part B the study will last for duration that the patient has a urine catheter inserted with a maximum of 24 hours. The setting of the study will be hospitalized patients who - for medical reasons unrelated to the study - have a urine catheter inserted.

4. STUDY POPULATION

4.1 Population (base)

Patient will be drawn from our hospital wards including but not limited to the general cardiology ward, cardiac care unit (CCU).

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

- 18 years and older
- Currently hospitalized
- Medical reasons unrelated to the study have a urine catheter inserted
- No specific urology problems
- Will and able to provide informed consent

4.2 Exclusion criteria

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

- Do not have a urine catheter inserted
- Are known to have chronically no diuresis (e.g., patients on dialysis) or other urology problems.
- A diuresis of <30ml per hour.

4.3 Sample size calculation

Part A will consist of 25 patients. Since this is the first-in-human study, to establish safety, and initial efficacy the investigators believe that this number will provide us meaningful information to collect scientific data for further development.
Part B will consist of 25 patients monitored with a manual monitor and 25 patients monitored with the FlowSure. The completeness of hourly urine production registration between the manual urine monitor and the FlowSure was compared using a two-group comparison of proportions. The study enrolled a total of 50 patients, with 25 patients using the manual urine monitor and 25 patients using the FlowSure. The completeness rate for the manual urine monitor was approximately 50% (P1 = 0.50), while the FlowSure data collection demonstrated a higher completeness rate of >90% (P2 = 0.90).

To assess the statistical significance of the difference in completeness rates, a significance level (alpha) of 0.05 was employed. The power (1 - beta) was set at 0.8. The pooled proportion (P) was calculated to be 0.70, and the standard error (SE) was estimated as 0.0948. Using a z-score of 1.96 for the selected alpha level, the difference in completeness rates was determined to be 0.40.

The effect size (ES), calculated by dividing the difference in completeness rates by the standard error, was found to be 4.216. Consequently, the study had a power of approximately 99% to detect the assumed difference in completeness rates between the manual urine monitor and the FlowSure monitoring device.

5. Randmization will be done using Castor EDC in a 1:1 ratio and patient will be randomized in blocks of varying size between 4 and 10 patients. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

FlowSure is a digital hanging scale that continuously weighs urine production over time, see detailed description under paragraph 6.

6. INVESTIGATIONAL PRODUCT

The automated FlowSure monitor is a digital hanging scale that continuously weighs urine production over time as urine flows through the urine catheter into the catheter bag underneath the patient's bed. The FlowSure visualizes the most recent hourly urine production on the screen of the device. Since the specific weight of urine is equal to water and thus one gram is equal to one millilitre, the increase in weight of the urine bag over time is a surrogate for urine production. FlowSure does not come into contact with the patient or

the patient's urine. The urine flows from the bladder through the catheter into the catheter bag under the patient's bed, while the catheter bag is attached to the FlowSure. Instead of attaching the urine bag to the bed, the urine bag is attached to the FlowSure, so that the weight can be continuously measured and recorded. Since the FlowSure does not come into contact with the patient or the urine, it is reusable after surface disinfection. The reusability will make FlowSure (cost) effective to operate.

6.1 Summary of findings from non-clinical studies

The FlowSure team has conducted a non-human study at the cardiology department of the Amsterdam UMC. In the study we have demonstrated the functionality and accuracy of the device in a mock set-up. In the set-up a Braun infusion pump was used to simulate a patient with diuresis and the investigational FlowSure device was test for operability, accuracy, and safety. The results demonstrated that the measurement with the FlowSure device is more accurate than the Braun infusion pumps that are currently in use in our hospital.
The infusion pump was set at a fixed rate of 50 millilitres per hour. The golden standard is the manual measurement with a measuring cup. The FlowSure accuracy was within 1% margin from the gold standard, whereas the margin for the infusion pump is up to 10%.

6.2 Summary of findings from clinical studies

This will be the first in human study to with the automated urine monitor FlowSure. Therefore, there is no previous experience to draw from, than a comparison with the manual method.

6.3 Summary of known and potential risks and benefits

There is no direct benefit for patients participating in the study. The societal/research benefit of the study lies in the potentially improved diuresis monitoring and registration in the medical record of the patient which will improve the quality and effectiveness of patient monitoring and therefore patient safety.

Risks: The foreseeable added risks associated with the use of the FlowSure in Part A are negligible as using the automated monitor will be additive to the manual measurements.
In part B patient will be monitored with either a manual monitor or the automated FlowSure monitor. If either monitor fails, the hourly urine production can be estimated by dividing the total urine collection since monitoring started by the hours that have passed since insertion of the urine catheter. The nurse will be able to read the urine production manually from the urine collection bag (without the measuring chamber) as the bag is transparent with an approximate graduation scale.
Risk-benefit analysis: Since the expected clinical-scientific benefit of this study is estimated as large and the clinical investigation is, in the opinion of the investigators, proportional to the

added risk associated with the use of the medical device, which is estimated as low, the overall risk-benefit profile of the study is favourable.

7. METHODS

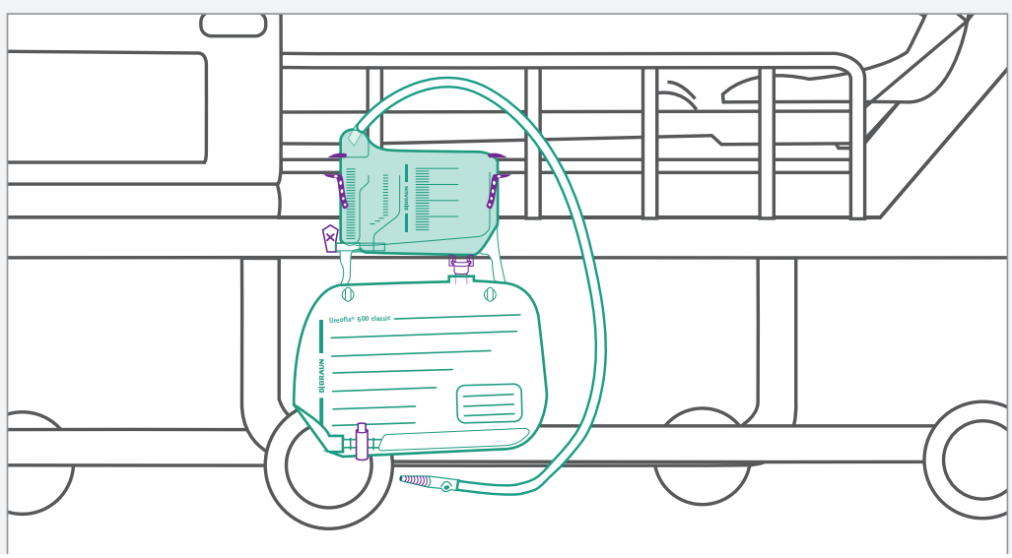
7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The primary outcome event in Part A will be the accuracy of urine measurement over two set time intervals (a nursing shift of 8 hours and a full 24-hours period) using manual monitoring and automated monitoring. The golden standard is the total urine production measured in a measuring cup by draining the collection bag in comparison with the new FlowSure device. The primary outcome in part B of the study will be the completeness of the hourly diuresis registration will be compared between the manual and automated measurement groups.

7.2 Study procedures

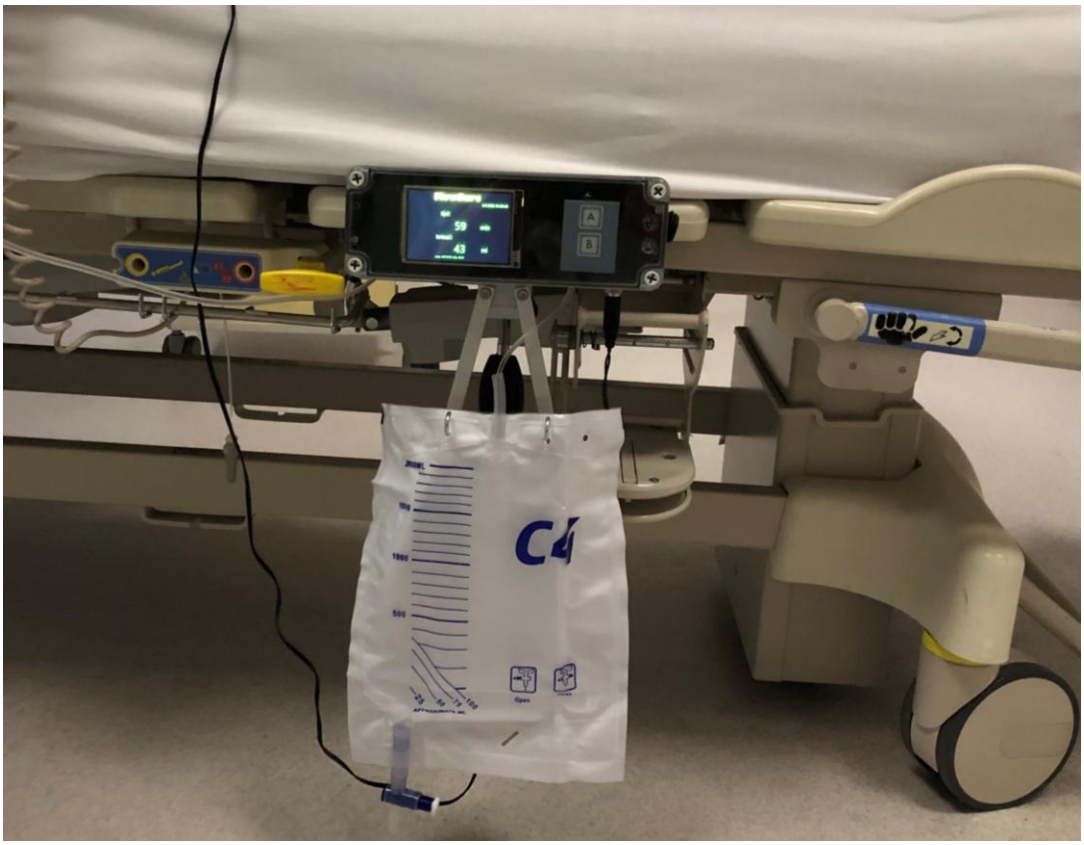
In part A, patient with a urine catheter will be monitored using the current standard of care with a manual measuring chamber and a collection bag below the measuring chamber. See image below.



The study procedure in part A is that the manual monitor displayed above will be attached to the investigational FlowSure device. The study subjects will thus be monitored both with the manual monitor and with the investigational FlowSure device.

In part B, in half of the study subject the manual monitor will be replace by investigational FlowSure device. These patients will receive a urine collection bag without a measuring chamber.

The urine collection bag has an approximate graduation scale, such that in case of device malfunction the nurse can read the urine production from the collection bag.



7.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. All data up until the point of withdrawal can be used

7.4 Replacement of individual subjects

Subject who withdraws consent, will be replaced until the sample size of the study has been reached without changing the randomization parameters, there will be no reuse of previous allocations. In addition, participants may also be replaced in cases where the primary endpoint cannot be evaluated due to demonstrable deviations from study procedures. Such cases include, but are not limited to:

- Disposing of the reference standard prematurely without the presence of a study investigator
- Demonstrably incorrect handling or operation of the investigational device.

7.5 Follow-up of subjects withdrawn from treatment

Subjects who have withdrawn from the study will be encouraged to report any new symptoms or events that may arise up until withdrawal, enabling prompt medical attention if needed.

7.6 Premature termination of the study

The criteria for prematurely terminating the study includes - but are not limited to the following Safety concerns - insufficient or inappropriate device functioning (e.g. when the device produces erroneous measurements that deviate >20% from the golden standard) or regulatory requirements.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance with section 10, subsection 4 of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and ADEs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, related to the use of the manual urine monitor or the investigational automated urine monitor FlowSure. All adverse events reported spontaneously by the subject or observed by the investigator, or his staff, during the 24 hour study period will be recorded.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death
- is life threatening (at the time of the event)
- requires hospitalisation or prolongation of existing inpatients' hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. The sponsor will report the SAEs in the form of a line listing at least every six months.

8.2.3 Adverse Device Effects (ADE)

Definition of 'Adverse Device Effect (ADE)': adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies

or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device This includes any event that is a result of a use error or intentional misuse. Legend for severity of ADE:

- Mild: Minor discomfort noticed but does not interfere with normal daily activity
- Moderate: Discomfort reducing or affecting normal daily activity
- Severe: Incapacitating with inability to work or perform normal daily activity

The sponsor will report expedited the following severe ADE through the web portal *ToetsingOnline* to the METC:

- Severe ADEs that have arisen in the clinical trial that was assessed by the METC
- Severe ADEs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining ADEs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all ADEs from the FlowSure device, accompanied by a brief report highlighting the main points of concern. The sponsor will report expedited all severe ADEs to the competent authorities in other Member States, according to the requirements of the Member States. The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases, the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.3 Annual safety report

In addition to the expedited reporting of severe ADEs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) severe adverse device events, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study

- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.4 Follow-up of adverse events

All AEs as defined in section 8.2.1 will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs as defined in section 8.2.2 need to be reported till end of study within the Netherlands, as defined in the protocol.

8.5 Data Safety Monitoring Board (DSMB) / Safety Committee

A DSMB is not needed given the very low risk of the study.

9. STATISTICAL ANALYSIS

9.1 Statistical analysis

To analyse the data, a two-group comparison of proportions will be performed using appropriate statistical tests, such as the chi-square test or Fisher's exact test. The null hypothesis (H0) assumes no difference in completeness rates between the manual urine monitor and the FlowSure device, while the alternative hypothesis (Ha) posits a significant difference in completeness rates. The resulting p-value will provide an assessment of the statistical significance of the observed difference.
Additionally, further exploratory analyses, such as subgroup analyses or regression modelling, may be conducted to investigate potential factors influencing completeness rates and to account for confounding variables.

The statistical software R and Rstudio will be utilized for data analysis, and a significance level of 0.05 will be used to determine statistical significance. The findings will be interpreted in conjunction with clinical considerations to guide conclusions regarding the comparative completeness of hourly urine production registration between the manual urine monitor and the FlowSure device.

9.2 Primary study parameter(s)

The primary outcome parameter of this study is the completeness of hourly urine production registration. It refers to the extent to which the two devices, the manual urine monitor and the FlowSure device, accurately capture and record hourly urine production data over a 24-hour period.

Completeness of hourly urine production registration represents the proportion or percentage of the total hourly measurements that are successfully recorded by each device.
For example, if a patient's urine output is measured every hour for 24 hours, the completeness rate indicates how many of these hourly measurements are successfully captured by the device.

In this study, the primary objective is to compare the completeness of hourly urine production registration between the manual urine monitor and the FlowSure device as registered in the electronic health record. The manual urine monitor has an assumed completeness rate of approximately 50% of hourly registrations, while Device B (FlowSure) is expected to have a higher completeness rate of over 90%.

By assessing the primary outcome parameter, the study aims to determine whether the FlowSure device significantly improves the completeness of hourly urine production registration, as compared to the manual urine monitor. The primary outcome will provide crucial insights into the devices' ability to accurately capture and register hourly urine production data, which is vital for monitoring and managing various clinical conditions.

The completeness of hourly urine production registration serves as a key indicator of the devices' reliability, usability, and potential clinical utility and safety. The primary outcome parameter will be analysed statistically, as described earlier, to assess the significance of the observed difference in completeness rates between the two devices.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted in adherence to the principles outlined in the Declaration of Helsinki, which is a set of ethical guidelines for medical research involving human subjects. The most recent version of the Declaration of Helsinki can be found at www.wma.net. Furthermore, the study will be conducted in accordance with the requirements of the Medical Research Involving Human Subjects Act (WMO) and other relevant guidelines, regulations, and acts governing clinical research. These include but are not limited to local and international regulations pertaining to the protection of human subjects, informed consent, confidentiality, data protection, and ethical considerations. The study protocol and procedures have undergone appropriate ethical review and approval by the relevant institutional review board or ethics committee. Stringent measures will be implemented to ensure the rights, safety, and well-being of the study participants throughout the trial.

10.2 Recruitment and consent

In this clinical study, hospitalized patients with a catheter will be recruited as potential participants. The medical team and research staff will collaborate to identify eligible patients who meet the study's requirements, specifically the inclusion and exclusion criteria.
Upon identifying potential participants, the research team will approach them to explain the study's purpose, procedures, potential risks, benefits, and expected outcomes. The initial contact and referral to the research team will be made by the medical team responsible for the the patient. The researchers will provide detailed information about the study in a clear and understandable manner, ensuring that all aspects of the study are comprehensively conveyed. Patients will be given ample time to ask questions and seek clarification.

In accordance with ethical guidelines and regulations, the research team will emphasize that participation in the study is voluntary and that patients have the right to decline participation or withdraw at any time without any negative consequences for their medical care.
The informed consent process will be conducted in a private and confidential setting to protect the participants' privacy and ensure a conducive environment for discussion.

Patients who express an interest in participating and meet the eligibility criteria will be provided with a written informed consent form. The research team will thoroughly explain the contents of the consent form, including the study's objectives, procedures, potential risks and benefits, confidentiality measures, and contact information for any questions or concerns. Patients will be encouraged to take their time to review the informed consent form and ask further questions before making a decision. If patients voluntarily decide to participate, they will be asked to sign the informed consent form, indicating their willingness to take part in the study. The research team will emphasize that signing the form does not waive any of their rights and that they can withdraw from the study at any point without penalty. The informed consent process will prioritize patient autonomy, respect for their decision-making capacity, and the protection of their rights and welfare. The research team will ensure that patients fully understand the nature of the study, the potential benefits and risks involved, and their rights as participants.

10.3 Benefits and risks assessment, group relatedness

In this clinical study, a comprehensive assessment of benefits and risks will be conducted to evaluate the potential impact of the research on participating patients. The benefits of the study include the opportunity to contribute to medical knowledge, potentially improving the care for hospitalized patients with a urine catheter. By participating, patients may indirectly benefit from the advancements in medical care that result from the study's findings.

The potential risks associated with the study are minimal. In case the automated FlowSure device does not register correct, urine production can always be checked by reading the changes from the urine collection bag. The research team will take appropriate measures to minimize risks by monitoring patients closely for any potential complications.

Throughout the study, the benefits and risks will be continuously evaluated and monitored to ensure the well-being and safety of the participants. Any unexpected adverse events or significant findings will be promptly addressed, and appropriate actions will be taken to mitigate risks and protect the participants' welfare.

10.4 Compensation for injury

The IRB has granted dispensation from the statutory obligation to provide insurance, because participating in the study is without risks. The sponsor has a liability insurance which is in accordance with article 7 of the WMO

10.5 Incentives

No incentives or compensation for participants will be used for the study.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling,storage and exchange of data and documents

All collected data will be securely stored and accessible only to authorized personnel involved in the study. Participant information will be anonymized and coded to maintain confidentiality, with any identifying details kept separate from the research data. Electronic data will be stored on password-protected servers, with regular backups and appropriate security measures in place to prevent unauthorized access. Physical documents will be stored in locked cabinets or rooms, accessible only to authorized personnel. The research team will strictly adhere to data protection laws and regulations, ensuring that all necessary approvals and permissions for data storage and handling are obtained (EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. (in Dutch: Uitvoeringswet AVG, UAVG). Data and documents will be retained for the required duration as per regulatory guidelines (, and their disposal at the end of the study will be conducted in a secure and confidential manner.

Data sharing and exchange will be done using coded participant information. Commercial party or parties that will bring the urinemeter to the market will be given access to encoded data in order to obtain (inter)national certification for healthcare use. This involves sharing data with certifying organizations such as a European Notified Body, the U.S. Food and Drug Administration, and foreign (government) institutions involved in approving the device for the local foreign market.

11.2 Monitoring and Quality Assurance

For the study, no formal study monitoring and quality assurance activities will be conducted due to several factors. Firstly, the study involves a low-risk intervention Secondly, the study is of limited duration and involves a relatively small sample size, making it logistically challenging and resource-intensive to implement formal monitoring and quality assurance measures. However, the research team will ensure strict adherence to the study protocol, good clinical practice guidelines, and relevant ethical standards to maintain the integrity of the data and protect the rights and safety of the participants. Regular communication and collaboration among the study team members will facilitate ongoing review and assessment of the study progress, thereby addressing any issues or concerns that may arise during the course of the research.

11.3 Amendments

All amendments will be notified to the METC that gave a favourable opinion.
A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial
- the scientific value of the trial
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority but will be recorded and filed by the sponsor.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

11.6 Public disclosure and publication policy

Data from the study will be publicly disclosed through presentations a scientific conference and through publications in peer-reviewed journals.

STRUCTURED RISK ANALYSIS

11.7 Potential issues of concern

a. Level of knowledge about the device's technology.

The mechanism of action of the investigational FlowSure device is known and straightforward. The investigational FlowSure device measures weight and translates weight to hourly urine production. The underlying assumption is that the molecular weight of urine is similar to water (in fact 1.007) and therefore close enough to translate grams of change to diuresis in millilitres.

b. Previous clinical experience with manual urine monitors:

There is extensive experience with the use of manual urine monitors in clinical care.

c. Potential for device-related injuries or harm:

There is no risk of device-related injury since the device does not touch the patient. Electrical safety and electromagnetic compatibility are secured as part of the local Convenant-Medisch-Technologie-authorization-procedure.

The investigational device demonstrates compliance with the internationally recognized ISO standard, specifically the IEC 60601-1, ensuring its compatibility and adherence to established industry requirements. FlowSure is housed in an IP67 certified housing from Fibox and is powered by a medical power supply. This enters the housing by means of a low voltage connector IP65 sealed by a screw socket. The on/off switch is IP65.

d. Compatibility with patient population:

The device will be used only in patients who already have, for medical considerations not related to the study, a urine catheter inserted.

e. Accuracy and reliability of device measurements:

Evaluating the accuracy and reliability of the device's measurements is paramount. In Part A of the study the investigation automated urine monitor FlowSure will be used in conjunction with standard manual urine production monitor. Patients will therefore be double monitored in Part A.

The protocol will transition to part B only when the investigational FlowSure device performance is within 15% difference from manual monitoring. In Part B of the study the investigational FlowSure device will replace the manual monitor. The nurse will be able to read the urine production manually from the urine collection bag (without the measuring chamber) as the bag is transparent with an approximate graduation scale.

f. User training and competence:

Nurses who take care of a study subject will receive written instruction prior to working with the investigational FlowSure device in order to avoid improper use, incorrect interpretations of results, or failure to identify potential risks associated with the device.

g. Maintenance and calibration requirements:
After each deployment the investigational FlowSure device will be checked for adequate function and damage.

h. Environmental considerations:
The housing of the device is waterproof and fully reusable.

i. Potential for misuse or user error:
The potential for misuse or error are small. The software of the investigational FlowSure device is programmed to recognize when the collection bag is emptied by the nurse and simply asks them to confirm their action. If the bag is removed from the device for a period of time and then placed back, the device will recognize this and continue its measurements. Incorrect measurements as a result of swinging of the urine collection bag is mitigated by the software algorithm through discarding large changes in subsequent measurements.
A potential for misuse is when the urine collection bag touches the ground and the bag does not hang on the device, the measurements are inadequate. Nurses are instructed to make sure that urine collection bag does not touch the ground.

j. Mitigation strategies and safety features:
If the investigations FlowSure device malfunctions or fails, the nurse can always revert back to reading the urine production manually from the urine collection bag (without the measuring chamber) as the bag is transparent with an approximate graduation scale.

11.8 Synthesis
Considering the above structured risk analysis, the risk for the study subjects in deemed low as in case of device malfunction the nurse can always revert to manual monitors. This results in an acceptable risk profile.

REFERENCES

Not applicable.