Protocol for non-CTIMPs

RAPPER – Relating Abdominal complications with Peritoneal Pressure Estimation and Reporting

To investigate the relationship between estimated intraperitoneal pressure and non-infectious PD-related abdominal complications

V1.5 – updated 21/09/2023

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Sponsor

Imperial College Healthcare NHS Trust is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Research Governance and Integrity Team
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Funder

This study receives no funding or financial support.

This protocol describes the RAPPER study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Full Form
eIPP	Estimated Intraperitoneal Pressure
ESRD	End-Stage Renal Disease
GCP	Good Clinical Practice
GSRS	Gastrointestinal Symptom Rating Scale
HRA	Health Research Authority
IPP	Intraperitoneal Pressure
PD	Peritoneal Dialysis
PET	Peritoneal Equilibration Test
PPF	Pleuroperitoneal Fistulas
PPV	Patent Processus Vaginalis
RRT	Renal Replacement Therapy

KEYWORDS
Chronic kidney disease
Peritonea Dialysis
Intraperitoneal pressure
Dialysate volume adjustment
Peritoneal leak
Hernia

STUDY SUMMARY

TITLE	Relating Abdominal complications with Peritoneal Pressure Estimation and Reporting
DESIGN	Prospective observational study
AIMS	To investigate whether estimated intraperitoneal pressure (eIPP) is correlated to non-infectious PD-related complications in end-stage renal failure patients
OUTCOME MEASURES	Measures non-infectious peritoneal complications including hernia, pleuroperitoneal fistulas (PPF), patent processus vaginalis (PPV), retroperitoneal leak and gastrointestinal symptoms since peritoneal dialysis catheter insertion
POPULATION	Patients treated with peritoneal dialysis
ELIGIBILITY	All adult patients both incident and prevalent to peritoneal dialysis
DURATION	Twelve months following study enrolment

REFERENCE DIAGRAM

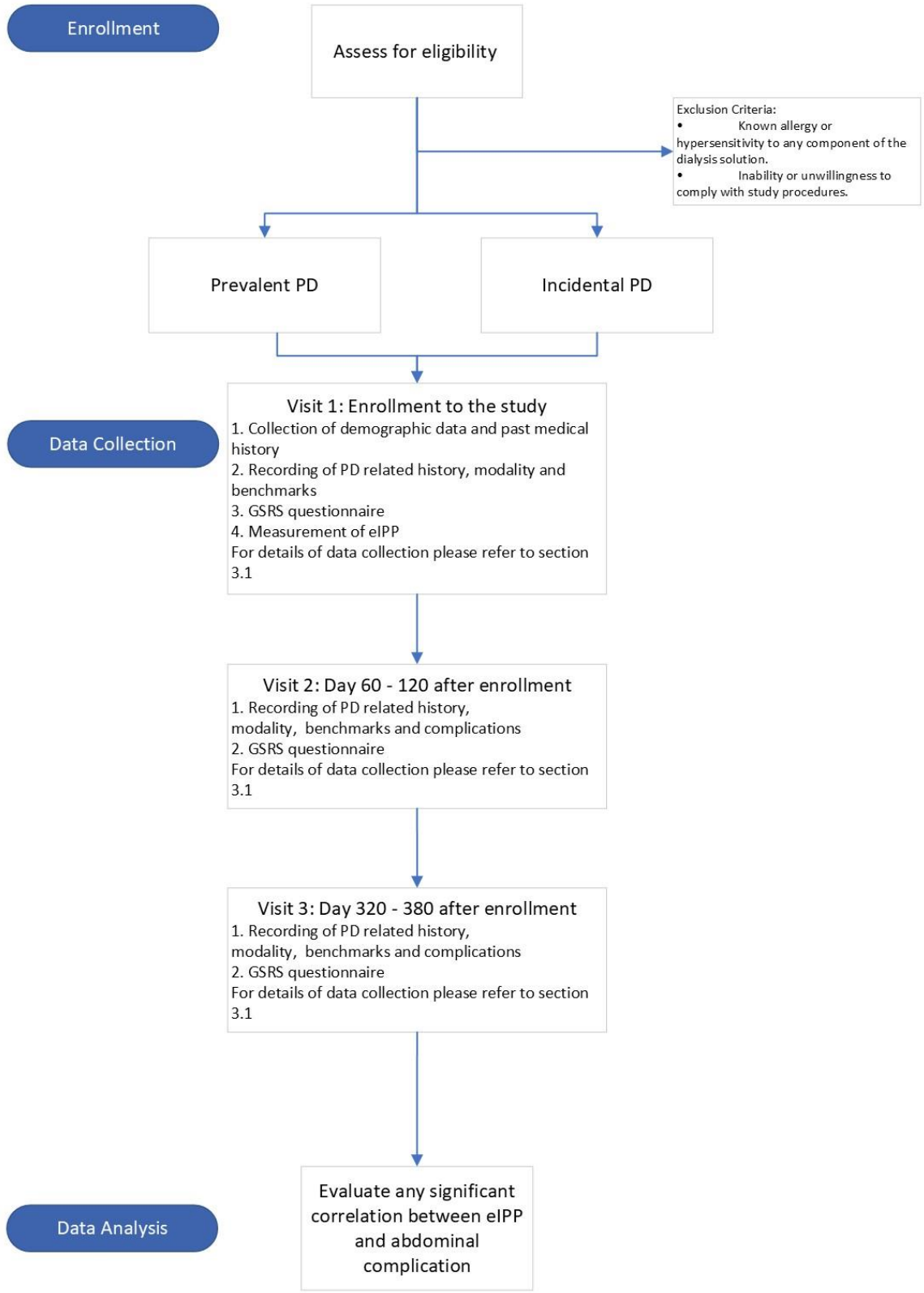

Figure 1 Study Flow Diagram

1. INTRODUCTION

1.1. BACKGROUND

Peritoneal dialysis (PD) is a commonly used renal replacement therapy for patients with end-stage renal disease, which accounts for 9% of renal replacement therapy in the world(1). Significantly lower cost, easy technique to learn at home and less nurse training being required make it a competitive alternative to haemodialysis. Despite the advantages, PD is associated with several complications, including peritonitis, catheter malfunction, and dialysate leaks, which can affect the patient's quality of life and survival(2,3). While studies have shown a relationship between intraperitoneal pressure (IPP) and various abdominal complications(4), invasive measurement of IPP, is logistically difficult, such that the practice of regular IPP measurement and with subsequent titration of dialysate volume is only recommended in children(5,6).

There are studies trying to simplify the measurements by calculating an estimated IPP (eIPP) with simple anthropometry measurements(7–10). Although they show good accuracy in estimating the actual IPP, there is a lack of studies to validate the correlation between eIPP and abdominal complications, including patient reported outcomes. The burden of gastrointestinal symptoms is high in patients treated with PD, the association with IPP is unclear but it is conceivable that high IPP may be associated with bloating and early satiety(11,12).

The aim of this research protocol is to investigate the relationship between eIPP and non-infectious abdominal complications in PD patients.

1.2. RATIONALE FOR CURRENT STUDY

- In peritoneal dialysis patients, there are established methods and equations to measure or estimate IPP(7,9,10,13)
- High IPP is related to reduced ultrafiltration (UF), hernias and peritoneal leak in PD patients(7).
- Current clinical practice does not include IPP measurement in adult patients(14).
- There is a lack of studies to investigate whether eIPP can predict non-infectious abdominal complications in PD patients.

2. STUDY OBJECTIVES

The primary objective of this research protocol is to investigate whether eIPP is correlated to non-infectious PD-related complications in end-stage renal failure patients.
The secondary objective is to assess the relationship of eIPP with patient-reported outcome measures particularly gastrointestinal symptoms.

3. STUDY DESIGN

This will be a basic science study involving procedures with human participants. It is a prospective observational study examining a prospective cohort of patients treated with peritoneal dialysis for kidney failure.

This will include two separate cohorts within the study, an incident cohort which will include all patients from the time of PD catheter insertion until 8 weeks after starting PD. A second prevalent cohort will include all patients treated with PD who are greater than 8 weeks from the start of dialysis. Patients will be recruited to either the incident or prevalent cohort.

A minimum of 150 patients will be recruited to both cohorts, so there will be a total of 300 participants.

The study will involve the delivery of two clinical assessments only, the measurements required to estimate IPP and the administration of the gastrointestinal symptom rating scale (GSRS) questionnaire at three time points. Aside from these additional assessements there will be no changes to clinical care and specifically any changes to intra-peritoneal dialysate volume will only be made by the clinical team caring for the patient without reference to the eIPP or GSRS.

3.1. STUDY MEASURES

The outline of the study was presented on session 3.

Initial Visit: Enrolment (Visit 1): Baseline demographic data will be recorded at the time of study enrolment including age, sex, chronic kidney disease (CKD) etiology, Charlson comorbidity index, history of polycystic kidney disease, previous abdominal surgery and presence of hernias, catheter technique placement.

The following anthropometric measurements are required:

1) Height: measured standing with shoes off
2) Weight: measured with shoes off and “empty” of dialysis fluid. If weighed with fluid in PD the fill volume should be substracted to give a “dry weight”
3) The distance from the decubitus plane the to mid-axillary line measured using the method described below:
    a. The decubitus plane is defined as the bed or couch with the patient lying supine (Figure 2 (A))
    b. The mid-axillary line is found by:
        i. The patient raises their arm above the head.
        ii. Locating the apex of the armpit, the deepest part of the armpit that the hand can reach.
        iii. The midaxillary line is the line parallel to the ground from the apex of the axilla downward along the lateral chest wall. (Figure 2 (B))
        iv. A level ruler is used to parallel to the ground to align its midline with the midaxillary line located in the previous step.
    c. Using another level ruler perpendicular to the ground to measure the distance from the midaxillary line to the decubitus plane

4) Waist circumference: measured with a tape measure wrapped above the iliac crests around the level of the umbilicus. See Figure 2 (C).

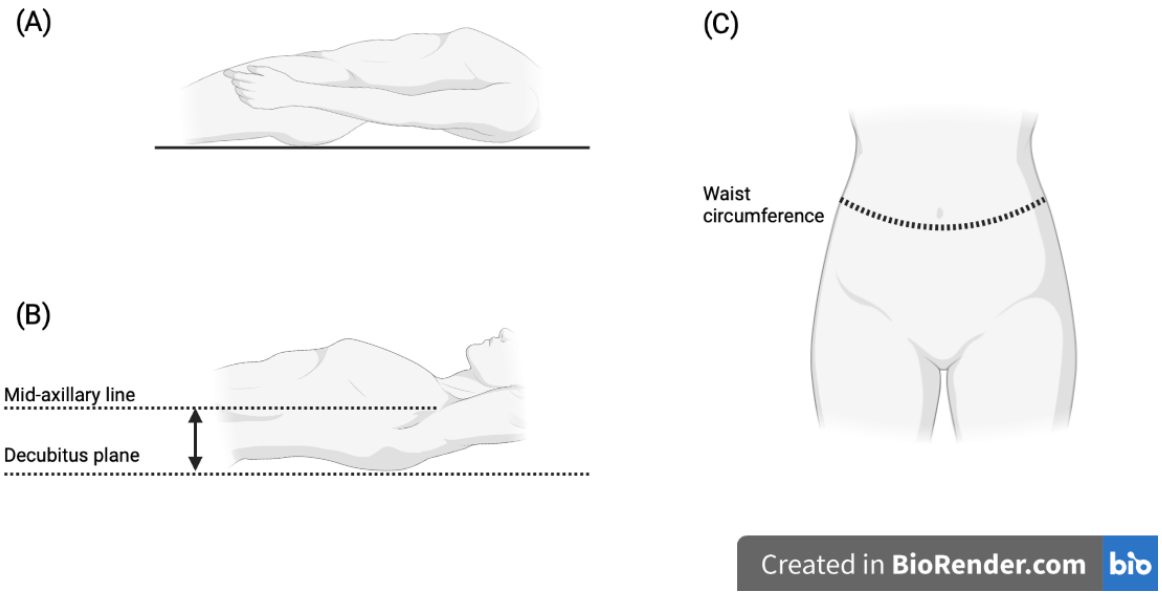

Figure 2 Measurements required to estimate IPP: The patient is placed fully supine on a couch (A). The couch defines the decubitus plane, while the mid-axillary line is identified- the distance between these two planes is measured (B). Waist circumference is measured above the iliac crests at the level of the umbilicus (C).

At Visit 1, 2 and 3 the following information will also be recorded: PD modality, prescribed day and night intra-peritoneal volume, adequacy and peritoneal function using peritoneal equilibration test (PET) data, number of peritonitis episodes, hernias, and leakages developed during PD treatment.

The GSRS will be administered at each Visit 1, 2 and 3 using paper questionnaires. At Visit 1 patients who have started dialysis will be asked to recall symptoms in the month prior to starting dialysis.

The estimated IPP will be assessed at Visit 1 using the equations included in Appendix 2 with the Li formula used for the primary outcome measure.

For the prevalent and incident cohorts. Visit 1 will take place at the time of study enrolment. Visit 2 will take place alongside a routine clinic visits between 60 to 120 days after enrolment (2-4 months). Visit 3 will similarly take place between 320 and 380 days (11-13 months after study enrolment.

Participants who refuse to fill in the GSRS questionnaire or

3.2. STUDY OUTCOMES

The primary outcome will be the incidence of non-infectious PD-related complications identified by the clinical team caring for the patient including the development of a new:

- Hernia
- Pleuroperitoneal fistula (PPF)
- Patent processus vaginalis (PPV)
- Retroperitoneal leak

The secondary outcome will be:

- changes in patient reported outcome measures on the GSRS at 3 and 12 months following study recruitment.referral for surgical fixation of non-infectious PD-related complications
- modality change to APD
- transfer to haemodialysis due to the non-infectious complications

During the period of 12 months from study enrolment. Radiological imaging is not required for confirmation nor is surgical fixation.

In Visit 2 and 3, participants who 1) refuse to fill in the GSRS questionnaire, 2) loss of adequate mental capacity to fill in the GSRS questionnaire, 3) refuse to consent clinicians to record their: PD modality, prescribed day and night intra-peritoneal volume, adequacy and peritoneal function using peritoneal equilibration test (PET) data, number of peritonitis episodes, hernias, and leakages developed during PD treatment, 4) defaulted follow-up visits, 5) become pregnant, and 6) received renal transplantation, will be recorded as early withdrawal from the study. Their reason to be withdrawal will be recorded. Data before withdrawal will still be used in outcome analysis. Participants who are withdrawing early from the study will receive same standard and schedule of care.

4. PARTICIPANT ENTRY

4.1. PRE-REGISTRATION EVALUATIONS

No pre-registration evaluations are required. All patients with kidney failure treated with peritoneal dialysis are eligible.

4.2. INCLUSION CRITERIA

- Age 18 years or older
- Diagnosis of end-stage renal failure requiring peritoneal dialysis as renal replacement therapy
- Ability to give informed consent and comply with study procedures.

4.3. EXCLUSION CRITERIA

- Known allergy or hypersensitivity to any component of the dialysis solution.
- Inability or unwillingness to comply with study procedures.

5. ADVERSE EVENTS

5.1. DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2. REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded

5.3.2 Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the London- West Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
CI email (and contact details below)

Please send SAE forms to: richard.corbett@imperial.ac.uk
Tel: xxx (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

All candidates will be followed up for 12 months following initial eIPP measurement. The formal end of this study will be 12 months after the eIPP measurement of the 150th incident cohort patient. No further recruitment to the prevalent cohort group will take place after the recruitment of the 150th incident patient. Incidental findings will not be recorded and reported in this study. Only the outcome mentioned in Section 3.2 will be recorded and analysed. Participants will be advised to report incidental findings to their GP and clinical care team as per local guidelines or standard of care.

7. STATISTICS AND DATA ANALYSIS

7.1. POWER CALCULATION

A small underpowered observational study of measured IPP Castellnaos et al(7), observed an event rate of 36% in a group of patient with high IPP compared with 17% in a group with low IPP. Using these estimates (with alpha of 0.05 with a power of 0.8, including a 0% drop out rate) a minimum of 146 patient will be recruited to the incident cohort. A similar number in the prevalent cohort should confirm any findings.

7.2. DATA ANALYSIS

7.3. Descriptive statistics will be used in assessing outcome measures.

7.4. DATASTORAGE

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1. ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the London-West Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2. CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3. CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Participants' information will be pseudonymised when possible. Only the pseudonymized form of data will be shared with researchers from other organizations, such as universities, NHS organizations, or companies involved in health and care research in the UK or abroad, in compliance with ethical and legal requirements.

Data collection, storage, and analysis will comply with data protection regulations, including the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018.

All participants' information will be stored securely and analysed using password-protected local computer with strict arrangements for access and use, ensuring that the information is used only for health and care research or to contact participants about future research opportunities. No cloud service will be involved.

8.4. INDEMNITY

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Resolution for NHS Trusts in England, which apply to this study (delete as applicable)

8.5. SPONSOR

Imperial College Healthcare NHS Trust will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6. FUNDING

No payment or funding is required by this study.

8.7. AUDITS

The study may be subject to audit by Imperial College Healthcare NHS Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Ka Chun Leung with contact details listed above.

10. PUBLICATION POLICY

- The study results will be disseminated through publication in peer-reviewed scientific journals, presentation at scientific conferences, and other appropriate channels.
- The study team will develop a summary of the findings in plain language to be made available to study participants, as well as to healthcare professionals and patient groups.
- All publications and presentations will acknowledge the contribution of study participants and comply with ethical standards for authorship.
- The study team will ensure that the results are communicated in a timely manner to stakeholders, including healthcare providers, policymakers, and patient groups.
- The study team will encourage and support the uptake of the study findings into clinical practice, where appropriate.
- The study team will comply with all relevant laws and regulations governing the dissemination of research findings.

11. REFERENCES

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APPENDICES

Appendix 1- Formulas for estimating Intra-Peritoneal Pressure

Given the evidence base the primary outcome is based upon the Li formula.

1) Castellanos formula(7):
eIPP = 5.820 + 0.462 x BMI + 0.387 x Charlson comorbidity index – 0.096 x months of PD – 0.002 x Daily usual UF

2) Scanziani formula(8):
eIPP = 1.0839 + 0.53 x BMI + 0.211 x fill volume (L)

3) De Jesús Ventura formula(9):
Fill volume = 2L: eIPP = –17.4 x (dialysate volume/body surface area) + 38.7
Fill volume = 2.5L: eIPP = –11.3 x (dialysate volume/body surface area) + 36.6
Fill volume = 3L: eIPP = – 8.7 x (dialysate volume/body surface area) + 37.2

- Body surface area will be calculated by Du Bois formula(15):
  - 0.007184 x height (cm)^0.725 x weight (kg)^0.425

4) Li formula(10):
Fill volume = 2L: eIPP = Waist (cm) * 0.193 – distance from decubitus plane to mid-axillary line * 0.907 + 8.613
Fill volume = 1.5L: eIPP = waist (cm) * 0.218 − distance from decubitus plane to mid-axillary line * 0.850 + 4.127