RESEARCH PROTOCOL

A randomized, controlled and open-label clinical study to evaluate the impact of INDIVIDUALIZED versus the conventional generic education on patient adherence to dialysis prescription in prevalent chronic peritoneal dialysis patients on automated peritoneal dialysis

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2021

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1.IDENTIFICATION

Scientific title

A randomized, controlled and open-label clinical study to evaluate the impact of an INDIVIDUALIZED education strategy tailored for learning style versus conventional education on patient adherence to dialysis prescription in prevalent chronic peritoneal dialysis patients on automated peritoneal dialysis

Scientific title (Portuguese)

Estudo clínico randomizado, controlado e aberto para avaliação do impacto da educação individualizada versus a educação convencional e genérica na adesão do paciente à prescrição de diálise em indivíduos prevalentes em diálise peritoneal automatizada

Public title

Impact of an individualized education tailored for the learning style on peritoneal dialysis patients

Scientific acronym

INDIVIDUALIZE

2.RESEARCH QUESTION

Does an individualized patient education tailored by learning style improve patient adherence to chronic peritoneal dialysis prescription?

3. THEORETICAL FRAME

Peritoneal dialysis patients are at high risk of technique failure and death (1-2). The causes are multifactorial but non-adherence to treatment is considered a key factor that negatively contribute in several different ways to negative

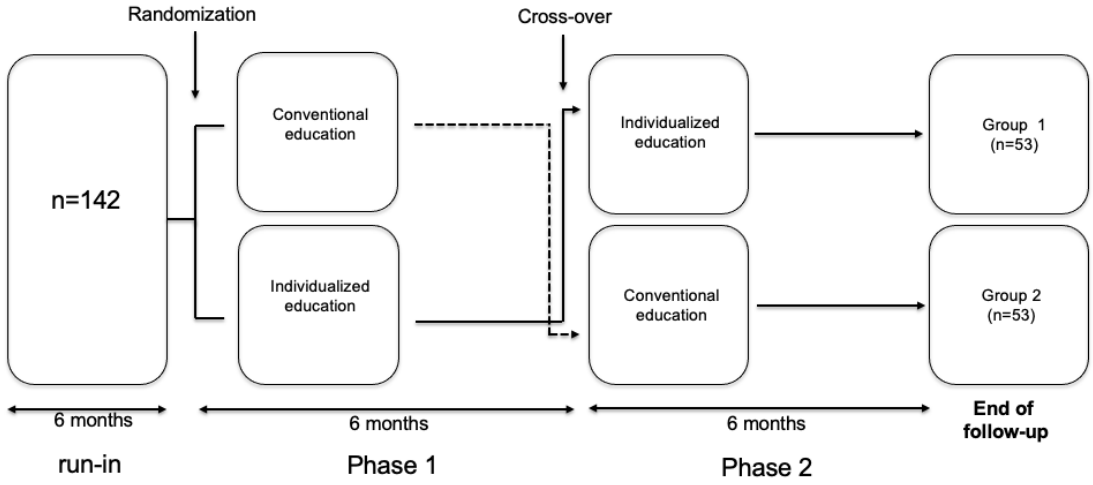
results. In 2014, a systematic review found that non-adherence is extremely common in PD and may reach more than 50% of patients depending on the definition criteria on non-adherence (3). Despite these alarming results, no study of our knowledge addressed a research question to tackle this problem with the proper scientific approach. In general, they limit to report the prevalence of non-adherence and associated factors.

It is intuitive to think that the most important strategy to try reducing non-adherence is by increasing patient and family awareness about the importance in following health professional prescription correctly. However, the process of education is complex because to transmit knowledge effectively is challenging. Recently, a Chinese randomized trial was unable to demonstrate a positive impact of regular retraining on peritonitis rates in contrast to the recommendations of the ISPD(4-6). However, more is not necessarily better, and it is important to note that the retraining offered was the same to all patients. However, more is not necessarily better, and it is important to note that the retraining offered was the same to all patients. Our hypothesis is that offering individualized education tailored by the learning style (classified accordingly to the VARK questionnaire) will improve adherence to dialysis prescription.

4. STUDY DESIGN

Randomized, open-label, cross-over and multicenter study. One hundred forty-two patients will be divided in 2 groups. After a 6-month run-in period the groups will be randomized

to receive conventional versus individualized education tailored by the type of patient's learning style.



Location study: Multicentric study in Brazil

Schedule of the study:

- Enrollment date of first participant: July 1st, 2021.
- Enrollment date of last participant: January 31st, 2022.

Hypothesis: Individualized patient education tailored by the learning style improves patient adherence to chronic peritoneal dialysis prescription.

5. INTERVENTION

Patients will be submitted to two types of education aiming to improve adherence to PD treatment. One is based on the conventional orientation used over the years to guide about the importance to follow medical prescription and the potential clinical consequences of missing dialysis sessions or time on dialysis at short and long term.

The conventional orientation occurs during the regular visits that happens every month in each PD clinic. This is

in line with national regulatory rules. During the consult the multidisciplinary kidney care team (doctor/nurse) explain to the patient in accessible language the possible consequences of not following dialysis prescription at home, including:

- Accumulation of waste products leading for example to hyperphosphatemia, hypercalemia and uremia.
- The adverse effects that the accumulation of the above-mentioned substances can cause on the cardiovascular system
- Inappropriate volume management and its consequences

The new intervention proposed will explain the same topics to the patients but in a manner adapted to the patient learning preference. After applying the VARK questionnaire the dominant learning style will be identified in five potential subgroups: a) read and write; b) aural; c) visual; d) kinesthetic; and e) finally a multimodal style (more than one prevalent style).

To score will be calculated as follows:

There are 16 questions with 4 potential answers, one corresponding to one learning style preference (VARK). The patient is allowed to choose more than one answer for each question. We then circle the letters that correspond to the patient's answer:

Question	a category	b category	c category	d category
3	K	V	R	A

We then count the number of each of the VARK letters circled to get the score for each category and define the preferred style of learning

Question	a category	b category	c category	d category
1	K	A	R	V
2	V	A	R	K
3	K	V	R	A
4	K	A	V	R
5	A	V	K	R
6	K	R	V	A
7	K	A	V	R
8	R	K	A	V
9	R	A	K	V
10	K	V	R	A
11	V	R	A	K
12	A	R	V	K
13	K	A	R	V
14	K	R	A	V
15	K	A	R	V
16	R	V	K	A

Total number of **V**s circled =	
Total number of **A**s circled =	
Total number of **R**s circled =	
Total number of **K**s circled =	

Measurement of adherence

All patients will receive a device (Claria® share-source) that provides daily online information about the therapy, including total time of dialysis, number of exchanges performed, and number of cycles performed

6. RANDOMIZATION

We will first identify all eligible patients from the participant clinics. These patients will then be assigned a unique number and in the sequence a sub-group will be randomly drawn (simple randomization), using a specific software, to be invited to study.

After acceptance and signature of the informed consent a new simple randomization process will occur to select whether the patient will start the trial in the group starting with conventional educational approach or with the new proposed intervention.

7. PRIMARY OUTCOME

The primary endpoint will be difference in patient adherence to dialysis prescription before and after intervention. This outcome will be measured as follows: the effective time on dialysis divided by the prescribed time in a timeframe of 30 days.

8. SECONDARY OUTCOMES:

- Percentage of patients using more than 90% of the prescribed PD solution
- Peritonitis rates (measured as episodes per patient-year) between interventions
- Metabolic control (anemia, potassium and phosphate) before and after intervention
- Blood pressure before and after intervention
- Hospitalization rates before and after intervention
- Health-related quality of life before and after intervention (SF-36)

9. TARGET POPULATION, INCLUSION AND EXCLUSION CRITERIA

The study will target chronic peritoneal dialysis patients in Brazil. Patients will be selected from 7 Brazilian PD centers. The pre-selected centers are:

- Hospital São Lucas de Porto Alegre – Porto Alegre RS - Brazil
- Fundação Pró Rim de Joinville - Joinville SC - Brazil
- Fundação Pró Renal de Curitiba - Curitiba PR - Brazil

- Santa Casa de Misericórdia de Curitiba – Curitiba PR - Brazil
- Renal Care Ltda – Brasilia DF Brazil
- Instituto do Rim Carrascossi – Araraquara SP Brazil
- Instituto de Doenças Renais - Porto Alegre RS - Brazil

Inclusion criteria

- Age > 18 years old
- Chronic PD (at least 3 months in therapy)
- On automated peritoneal dialysis
- Sign the informed consent

Exclusion criteria

- Illiteracy
- Blindness
- Assited peritoneal dialysis (patients that need a family member or caretaker to make the dialysis procedure)

10.0 SAMPLE SIZE:

- The calculation was performed using STATA 14, with the command *power pairedmeans* Alpha was set to 0.05 and Beta to 0.80
- Pre-intervention adherence: patients perform in average 80% of the prescribed time Post-intervention adherence: patients perform in average 90% of the prescribed time Standard deviation of the differences: 25
- Sample size before drop-out: 106
- Estimated drop-out (using the BRAZPD II data as reference): 35% in 1 year

11. STATISTICAL ANALYSIS PLAN

Continuous variables will be expressed as mean ± SD or median and interquartile range, while categorical variables (e.g., gender, race, etc) will be expressed as frequencies or percentages.

Primary outcome: Paired t test

Secondary outcomes: Paired t test, Poisson regression, logistic regression or Cox regression analysis according to the type of outcome

Missing data handling: Imputation procedures will not be applied on missing data. If an individual leaves the study during the phase 2 period, this patient will not be considered as having completed the study, but his/her available data might be used for relevant analysis.

12. STUDY´S IMPLEMENTATION PLAN AND PROTOCOL

Patients included in the study will initially perform a test to identify his/her learning preference. For this we will use a questionnaire called VARK, freely available to anyone on https://vark-learn.com/. This quick questionnaire will categorize the preference of learning based in 4 topics: visual, aural, read/write and kinesthetic. The supplementary file 1 brings the full questionnaire that will be used in the study including the values attributed to each potential answer within the 4 type of preferences.

Researchers will record the information in hard copy format; and the data will be entered in a centralized database, specially designed for the study. All stored data will be anonymized to don't allow patient identification.

Laboratory procedures

The study protocol **does not** ask for any collection of biological samples. Laboratory results will be exported from the regular clinic system and will be restricted to the routine battery of exams normally performed for PD patients according to the local health system regulation.

Data quality assurance

Researchers will receive training on how to fill out the case report forms for all information that aren't automatically provided electronically (remotely) by the cycler. An independent data quality assurance audit can be set up if needed.

Patient withdrawal from the study: Patients may be withdrawn from the study for any of the following reasons:

1) Termination of the study
2) Kidney transplant
3) Switch from PD to HD
4) Death
5) Unwillingness to continue
6) Transfer to a renal unit not belonging to a participating study center.
7) Recovery of RRF

Visit's procedures:

A. Run-in: Screening visit (n° 0):

During the screening visit, the following procedures should be completed:

1) Patient must sign the informed consent form.
2) Those patients fulfilling inclusion criteria and not having exclusion criteria will be randomly allocated and will be assigned an identification number.

3) A clinical data record and a physical examination should be made. Physical examination of the patient includes weight, height, presence or absence of edema, systolic blood pressure, diastolic blood pressure, resting heart rate and respiratory rate.
3) Record all the drugs the patient receives, including dosages and administration routes.
5) Record daily ultrafiltration as well as long-dwell Exchange UF, both in milliliters.
6) Record all lab results of the current month from the patient's file.
7) Dialysis prescription: time on cycler, total volume, dwell volume, number of exchanges and glucose concentration

B. Phase 1 (Visits 1 to 6): During these visits the investigators will perform the following tasks:

1) Physical examination of the patient, including: weight, height, presence or absence of edema, systolic blood pressure, diastolic blood pressure, resting heart rate, respiratory rate, and temperature.
2) Record of all medications given to the patient, including generic name, dosage, route and frequency.
3) Record of all relevant information such as body weight, height, lab tests results, current prescription of APD, generic name of the dialysis solution, volume, and number of exchanges.
4) Record of peritonitis events, date, gram test, cytochemical test, and culture results, as well as antibiotics used.
5) Measurement of baseline health-related quality of life (SF36).
6) Apply the study intervention according to the group allocated during the randomization process

7) Dialysis prescription: time on cycler, total volume, dwell volume, number of exchanges and glucose concentration

C. Phase II (Visits 7 to 12): During these visits the investigators will perform the following tasks:

1) Physical examination of the patient, including: weight, height, presence or absence of edema, systolic blood pressure, diastolic blood pressure, resting heart rate, respiratory rate, and temperature.
2) Record of all medications given to the patient, including generic name, dosage, route and frequency.
3) Record of all relevant information such as body weight, height, lab tests results, current prescription of APD, generic name of the dialysis solution, volume, and number of exchanges.
4) Record of peritonitis events, date, gram test, cytochemical test, and culture results, as well as antibiotics used.
5) Measurement of baseline health-related quality of life (SF36).
6) Apply the study intervention according to the group allocated during the randomization process
7) Dialysis prescription: time on cycler, total volume, dwell volume, number of exchanges and glucose concentration

D. Closing visit (n°13):

1) Physical examination of the patient, including: weight, height, presence or absence of edema, systolic blood pressure, diastolic blood pressure, resting heart rate, respiratory rate, and temperature.
2) Record of all medications given to the patient, including generic name, dosage, route and frequency.

3) Record of all relevant information such as body weight, height, lab tests results, current prescription of APD, generic name of the dialysis solution, volume, and number of exchanges.
4) Record of peritonitis events, date, gram test, cytochemical test, and culture results, as well as antibiotics used.
5) Measurement of baseline health-related quality of life (SF36).
6) Dialysis prescription: time on cycler, total volume, dwell volume, number of exchanges and glucose concentration

13. BUDGET

Devices:

Baxter Product(s):	**Units**	**Unitary value** (Reais)	**Total** (Reais)
Product Name/Code	Sharesource		
Amount Requested	142	1000,85	**142.120,7**

Personnel – (i.e., percentage of time)				
	Year 1 (R$)	**Year 2** (R$)	**Year 3** (R$)	**Total** (R$)
Investigators:	24.000	24.000	24.000	72.000
Research Assistants:	6.000	6.000	6.000	18.00
Total personnel expenditure:	30.000	30.000	30.000	**90.000**

Other Related Expenses – IRB/REB/IACUC Review, Travel, Publications, Database Leasing, etc.				
	Year 1 (R$)	**Year 2** (R$)	**Year 3** (R$)	**Total** (R$)
Travel:	-	-	-	-
➢ International flight	-	5.000	5.000	5.000
➢ Housing	-	5.000	5.000	5.000
➢ Food and local transportation	10.000	-	-	-
Publication(s), e.g. poster design/printing, manuscript writing/editing:				
➢ Publication fee	-	5.000	5.000	10.000
Other Expenses:				
Creation and maintenance of a dedicated study website/social media	4.000	4.000	4.000	12.000
STATA MP6 software V.16	10.000	-	-	10.000
Data analyst	6.000	6.000	6.000	12.000
Total	30.000	20.000	20.000	**80.000**

14. ETHICAL ISSUES

a) Research ethics committee: The main investigator will be the final responsible for supervising the research on a

daily basis, as well as for all the ethical issues of the study.

b) The research protocol and the informed consent must be submitted to the ethics committee for independent evaluation, and to other ethical committees as required.

c) The investigator must have a written approval of the protocol and the informed consent prior to the beginning of the study. No study should be started until approval of the research ethic committee is obtained by the main researcher.

d) The main investigator is responsible for informing the research ethics committee of amendments or termination of study.

e) The informed consent form must include all the elements required by the research ethics committee, local regulatory agencies.

f) The study follows the Declaration of Helsinki II

g) Patient information, confidentiality and consent. After the study has been explained and fully understood, the patient is required to sign a consent form before entering the study. Patient information, including medical records and test results, will be kept confidential. In order to maintain this confidentiality, all patient information and study data will be coded under a random identifier that cannot be linked to you personally.

h) Access to the source of information is limited to the main investigator –who guarantees this-, the monitor of the study, and the regulatory authorities or auditors. This is guaranteed by the main researcher.

15. ADMINISTRATIVE STRUCTURE OF THE STUDY

Responsibilities of the researchers:

a) Ensure compliance with the protocol. The investigator should not implement any deviation from, or changes of the protocol without agreement and approval from the ethics committee after evaluation of the proposed modification.
b) Provide the ethics committee with fast and timely information about:
- Any deviation or changes from the protocol, implemented to avoid a risk for subjects participating in the study.
- Any change that might increase the risk for subjects participating in the study and/or significantly obstruct the study´s progress.
c) The investigator will ensure the proper custody of documents deemed critical for the study. Documents will be kept according to regulatory agencies requirements. Documents will be kept for 5 years after the end of the study.
d) Inform the patient´s primary healthcare team, when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

Responsibilities of the local investigator:
a) The local investigator will ensure a proper selection process in accordance with the study protocol.
b) He/she will make sure that the subject was fully informed of the purpose, protocol, and procedure of the study. He/she will obtain an informed consent from the subject.
c) He/she will ensure a strict follow-up of the protocol.
d) He/she will document and keep confidential and safe the following: informed consent, source documents, and adverse event report forms and peritonitis forms. He/she also will provide access to patients´ clinical history.
e) He/she will ensure the accuracy, reliability, totality, legibility and opportunity of the data recorded on the Case

Report Form. Data on case report forms is consistent with the source documents. After a patient is withdrawn or completes the study, the original CRF form must be submitted to the monitor of the study or designated representative; copies of the CRF will be kept at the source of the data.

f) He/she will facilitate the data audit processes conducted by personnel authorized by the main investigator or the regulatory agencies.

g) He/she will safely send the CRFs and the adverse event/peritonitis report forms to the central office of the study.

h) He/she will keep at the site of the study, safe and confidential, all the study´s information and documents for the established period of time.

i) He/she will ensure the processing of all adverse events potentially related to the study, informing local regulatory.

j) A written informed consent should be obtained from every patient once the study protocol and the informed consent are approved by the ethics committee.

Responsibilities of the local coordinator.

a) He/she will check all the documentation sent by the sponsor and the main investigator.

b) He/she will keep organized and updated files with all the study´s documents.

c) He/she will develop and/or implement operating procedures to guarantee the perfect achievement of the study.

d) He/she will elaborate a plan of visits, including the activities for each of them.

e) He/she will confirm that the information obtained is accurate, complete and verifiable.

f) He/she will coordinate monitoring dates with the sponsor as well as the logistics required for this process.
g) He/she will help to write follow-up reports for the research ethics committees.
h) He/she will keep the reports on the study progress updated.
i) He/she will verify that the patients´ rights and welfare are protected during the study.

Monitor

The Monitor´s functions include:

a) Provide investigators / local investigators / local coordinators with all the forms previously approved for the study, as well as with copies of the protocols.
b) Ensure the compliance with the protocol and with the monitoring / audit processes of investigators / local investigators / local coordinators, in accordance with best clinical practices guidelines.
c) Review the case report forms to determine their validity, accuracy, and duly completion; and develop processes to resolve questionable issues.
d) Keep files with all the original Case Report Forms maintaining the confidentiality of the data.
e) Provide clinical research information when requested by the regulatory agencies.

16. SPONSORS

a) Primary sponsor: Escola de Medicina – Pontifícia Universidade Católica do Paraná

b) Secondary sponsor: Medicina Renal e Interna Serviços Médicos e Pesquisa Clínica Ltda

c) Supporting source: Baxter Healthcare Brazil

17.0 REFERENCES

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18. SUPLEMENTARY FILES

18.1 IDENTIFICATION OF PATIENTS' LEARNING STYLE

For the identification of learning style preferences we will use the VARK (visual/ aural/read/kinesthetic) questionnaire. The questions, answers and respective points attribution are as follow (the letters following each answer are illustrative and not shown to the patient during the test):

I want to learn about a new project. I would ask for:

a) an opportunity to discuss the project.
b) diagrams to show the project stages with charts of benefits and costs.
c) a written report describing the main features of the project.
d) examples where the project has been used successfully.

When learning from the Internet I like:

a) interesting design and visual features.(V)
b) videos showing how to do or make things.(K)
c) audio channels where I can listen to podcasts or interviews.(A)
d) interesting written descriptions, lists and explanations.(R)

I want to find out more about a tour that I am going on. I would:

a) read about the tour on the itinerary.(R)
b) look at details about the highlights and activities on the tour.(K)
c) use a map and see where the places are.(V)
d) talk with the person who planned the tour or others who are going on the tour.(A)

I have a problem with my heart. I would prefer that the doctor:

a) described what was wrong.(A)
b) gave me something to read to explain what was wrong.(R)
c) showed me a diagram of what was wrong.(V)
d) used a plastic model to show me what was wrong.(K)

I prefer a presenter or a teacher who uses:

a) diagrams, charts, maps or graphs.(V)

b) handouts, books, or readings.(R)
c) question and answer, talk, group discussion, or guest speakers.(A)
d) demonstrations, models or practical sessions.(K)

I have finished a competition or test and I would like some feedback. I would like to have feedback:
a) using examples from what I have done.(K)
b) using graphs showing what I achieved.(V)
c) using a written description of my results.(R)
d) from somebody who talks it through with me.(A)

I want to learn how to take better photos. I would:
a) use examples of good and poor photos showing how to improve them.(K)
b) ask questions and talk about the camera and its features.(A)
c) use the written instructions about what to do.(R)
d) use diagrams showing the camera and what each part does.(V)

When I am learning I:
a) use examples and applications.(K)
b) see patterns in things.(V)
c) like to talk things through.(A)
d) read books, articles and handouts.(R)

I want to assemble a wooden table that came in parts (kitset). I would learn best from:
a) written instructions that came with the parts for the table. (R)
b) advice from someone who has done it before.(A)
c) watching a video of a person assembling a similar table.(K)
d) diagrams showing each stage of the assembly.(V)

I want to learn how to play a new board game or card game. I would:
a) use the diagrams that explain the various stages, moves and strategies in the game.(V)
b) watch others play the game before joining in.(K)
c) listen to somebody explaining it and ask questions.(A)
d) read the instructions (R)

I want to learn to do something new on a computer. I would:
a) read the written instructions that came with the program. (R)
b) follow the diagrams in a book.(V)

c) start using it and learn by trial and error.(K)
d) talk with people who know about the program.(A)

I want to save more money and to decide between a range of options. I would:

a) consider examples of each option using my financial information.(K)
b) read a print brochure that describes the options in detail.(R)
c) talk with an expert about the options.(A)
d) use graphs showing different options for different time periods.(V)

I want to find out about a house or an apartment. Before visiting it I would want:

a) a plan showing the rooms and a map of the area.(V)
b) a printed description of the rooms and features.(R)
c) a discussion with the owner.(A)
d) to view a video of the property.(K)

When choosing a career or area of study, these are important for me:

a) Applying my knowledge in real situations.(K)
b) Working with designs, maps or charts.(V)
c) Communicating with others through discussion.(A)
d) Using words well in written communications.(R)

I need to find the way to a shop that a friend has recommended. I would:

a) ask my friend to tell me the directions.(A)
b) find out where the shop is in relation to somewhere I know.(K)
c) use a map.(V)
d) write down the street directions I need to remember.(R)

A website has a video showing how to make a special graph or chart. There is a person speaking, some lists and words describing what to do and some diagrams. I would learn most from:

a) watching the actions.(K)
b) seeing the diagrams.(V)
c) reading the words.(R)
d) listening.(A)

18.2 SCREENED PATIENTS FILE FORM

Initials	CH	Screening date	Random. date	Random group	ID #	Date of first day of treatment

18.3 STUDY PROCEDURES CHECKLIST FORM

Procedure Visit	Screening	Run-in	Phase 1	Phase 2	Final
Informed consent	X				
Intervention			X	X	
Randomization		X			
Vital signs		X	X	X	X
Physical examination		X	X	X	X
UF document.		X	X	X	X
Clinical history		X	X	X	X
Adverse events documentation		X	X	X	X
Peritonitis documentation		X	X	X	X
Hospitalization documentation		X	X	X	X
QoL measurement		X	X	X	X