

The logo for INNOVCare, featuring the word "INNOVCare" in a sans-serif font. The "O" is stylized with three orange dots arranged in a triangle around it.

WP7: METHODOLOGY REPORT

The effects of a case management approach on the quality of life of rare disease patients in Salaj, Romania: a randomised control trial of efficacy

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This project is co-funded by the European Union

Call for Proposals VP/2014/008; EaSI PROGRESS, DG Employment, Social Affairs and Inclusion

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1. INTRODUCTION

The INNOVCare project is funded under the EaSI PROGRESS programme of the European Commission's Directorate General of Employment, Social Affairs and Inclusion. The project concept was developed as a response to a call for proposals for social policy innovations supporting reforms in social services (EaSI, 2014). The INNOVCare consortium decided to contribute to this call by 'proposing and testing an innovative care pathway for the social inclusion of a EU marginalised group of over 36 million EU citizens and households affected by rare diseases and proposing up-scaling roadmaps that can increase the model's impact to other 80 million vulnerable EU citizens (people with disabilities) and beyond (i.e. chronic diseases' (INNOV-CARE, 2014).

The guidelines for the call for proposal out rightly encouraged the use of 'social policy experimentation as a method for testing and evaluating innovative solution with a view of scaling up' (EaSI, 2014). In response, the INNOVCare project consortium planned the implementation of social policy experimentation into the activities of the project.

The intervention will be implemented in the form of an experiment and analysed aims at 'linking health services to employment and the social and support services that a rare disease patient uses on a daily basis (school, transport, leisure services etc.), ensuring the transfer of information and expertise between service providers. The care pathway also centralises the coordination of care through a resource centre for rare diseases and regional case managers, in an effort to relieve the burden of care management for people living with a rare disease and their families' (INNOVCare, 2016) thereby improving their quality of life.

The exact intervention will be designed based on available literature, the results of focus groups with rare disease patients and their families from another region in Romania, results of a EU-wide survey on the quality of life of rare disease patients carried out by the European Organisation for Rare Diseases (EURORDIS)¹ and consultations with experts working with rare disease patients in the intervention site in the county of Salaj in Romania. Further input comes from the series of European events and workshops organised or co-organised by the INNOVCare project to network rare disease patients' associations, care providers and policymakers on the delivery and improvement of health and social services for this group. The intervention will be defined following the 'logic model' (resources/inputs, activities, outputs, outcomes and impact). It will be implemented following a basic two-condition repeated-measures design / rotation design which ensures that all the participants in the study receive the intervention at some point during the implementation. This is important due to the vulnerability of this target group as it would be considered unethical to withhold treatment from any participant.

The main question guiding the impact analysis will therefore be: how does this intervention change the lives of those who benefit from it?

¹ EURORDIS is an organisation in France making up one of the 7 project partner organisations in the INNOVCare project. The other project partners include: The Ministry of Health, Social Services and Equality, Spain (overall project coordinators; NoRo Resource Centre, Romania; County of Salaj, Romania, Karolinska Institutet, Sweden, Inštitut za Ekonomska Raziskovanja, Slovenia and the Centre for Social Innovation (ZSI), Austria.

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One of the main responsibilities of ZSI in this project is to develop the methodological framework and evaluation design for the social policy experimentation. Moreover, ZSI is responsible for the development of indicators, data collection tools, the statistical/impact analysis and the qualitative analysis of the intervention. The following report describes these tasks in detail. It starts off by presenting literature on 'quality of life' and presenting some indicators for measuring it. It goes on to briefly describe the main aspects of the intervention based on the logic model of intervention; which is a description of the exact services that will be provided by INNOVCare's case managers as well as the expected inputs, outputs and outcomes of the intervention in general. The evaluation strategy which is in this a social experiment (based on a basic two-condition repeated-measures design / rotation design) is then described in details including the design, participants, apparatus and procedure. The statistical techniques that will be used to measure the impact of the intervention (descriptive statistics and inferential statistics) are also described.

2. QUALITY OF LIFE OF RARE DISEASE PATIENTS

Quality of life is not a clear cut concept that can be adapted and readily tailored to the needs of patients with rare diseases. Rather, quality of life and even more so its measurement is a contested concept that lacks a clear definition. Indicators of quality of life are often used as the basis for deciding whether or not for example an intervention or a policy reform should be continued.

'Quality of life has become a driving force in service design, delivery and outcome evaluation across medicine and social care. The quality of life of 'patients'/'service users' is now routinely advocated as a measure of the 'quality' and 'value for money' of services' (Rapley, 2003, p.74).

However, it is often questionable when such a subjective indicator is treated as an objective one. Wellbeing and living a good life, indicators of quality of life, highly depend on a person's individual value judgment. At the same time, what is considered a good life also depends on value judgements and culture within a society. In support of this, Gasper (2010) argues that 'different purposes contribute to the formation of different concepts and judgements of wellbeing and life quality' (Gasper, 2010, p.359). Evaluating a person's quality of life therefore means making value judgements about someone's entire life or aspects thereof which might have serious political, social and personal consequences. As a result, careful considerations need to be made when defining and measuring quality of life especially in relation to vulnerable groups such as rare disease patients.

Within the quality of life literature, there is an ongoing debate as to whether to use objective or subjective indicators. Objective indicators refer to 'measurable social facts' insofar as they are seen independent from a person's own evaluation or value judgment. These 'facts' include for example health, poverty or unemployment rates. Philipps (2006) suggests that these 'social facts' should rather be called 'collectively subjective measures' (Phillips, 2006, p.233), as they, like individual self-assessment, rely on collectively agreed criteria. Noll (1996) points out the value judgment that is inherent when using objective indicators: 'using objective indicators starts from the assumption that living conditions can be judged as being favourable or unfavourable by comparing real conditions with normative criteria like values or goals. An important precondition, however, is that there is political consensus first about the dimensions that are relevant for welfare, second a consensus about good and bad conditions and third about the direction in which society should move (Noll 1996, p.5).'

By contrast, 'social indicators' rely on the subjective perception of one's life situation (Noll, 1996). The core idea is that individuals can best judge their individual life situation. Scandinavian welfare research tradition highly criticises self-assessment of one's own satisfaction and the resulting use of these

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measurements as political measures of quality of life, highlighting that judgments about individual's life situations hugely depend upon 'how well they have adapted to their present conditions' (Erikson, 1993, p.77) – however 'good' or 'bad' they might be. This kind of adaption to living conditions and especially when they would otherwise be considered as 'bad' conditions is referred to as the 'satisfaction paradox' or cognitive dissonance (Rapley, 2003, p. 31).

Other projects dealing with integrated care like Esther² and Prisma³, define improving the quality of life of their target groups as improving their autonomy. Such projects seek to implement an emancipatory approach which is explicitly normative: the participant is at the centre of the programme and together with his or her network and caregivers, is encouraged and sought after to communicate his/her needs with the aim of improving the patient's quality of life. As such, INNOVCare could draw from these projects specifically asking questions like: 'What does the person living with a rare disease need and/ or want?'; 'Is this best for this person?' 'What are they missing at the moment?' and 'what they would need/ wish for in order to improve their quality of life?'

Even when asking such questions, as INNOVCare has to deal with both adults and children, some ethical concerns surface regarding who is the best person suited to answer such questions on behalf of children who cannot or are unwilling to speak for themselves. This raises numerous ethical concerns and questions for example whether it is at all possible to measure children's 'real' quality of life or even whether quality of life is an aspect that can be considered to affect children at a young age directly. Literature suggests that when evaluating children's quality of life, instruments need to 'consider children's emerging sense of self, cognitive capacity and emotional awareness' (De Civita et al. 2005, 659). Furthermore, Rapel (2003) indirectly highlights the importance of including children's voices in quality of life assessment by repeatedly asking the question 'whose quality of life is it?' in his suggested ethical questions to be considered when developing and evaluating a quality of life study (see Table 1 below).

² <http://plus.rjl.se/infopage.jsf?nodeId=31383>

³ <http://www.prismaquebec.ca/>

- Whose quality of life is it?
 - Who is/are the expert(s) on QOL in the population I wish to study: academics or the people themselves?
 - What is the relationship between the theoretical/operational definition of QOL used by the measures that I am going to employ and the everyday understandings of QOL of the people to whom I am going to administer them?
 - What are the everyday understandings of QOL of the people I am working with?
 - What procedures or methods might I adopt that would assist me to find out?
 - Whose quality of life is it anyway?
 - If everyday understandings are different from those proposed by the measure I intend to use, what are the ethical issues here?
 - What direct and specific benefits to my research participants will flow from this quality of life project?
 - If I cannot specify such direct benefits, in advance, what are the ethical implications of this failure?
 - Is the research ‘mainstream’ or ‘emancipatory’? If ‘mainstream’ how could it be redesigned to give a genuine voice to my participants?
 - What harm (physical, emotional, psychological) might my study of the quality of their lives cause to my participants?
 - What indirect benefits may accrue to participants/the wider research community from my quality of life study?
 - Whose quality of life is it anyway?
-

TABLE 1: SOME ETHICAL QUESTIONS TO CONSIDER WHEN DEVELOPING AND DESIGNING A QOL STUDY (RAPLEY, 2003, P.81)

In conclusion, drawing from the findings of this literature review, INNOVCare could consider ‘autonomy’ as the main goal when talking about improving the quality of life of people living with rare diseases. At the same time, the autonomy and quality of life of families, care givers and the social network of persons living with a rare disease need to be taken into consideration. There might be different or even conflicting interests that need to be examined. As a result, relevant indicators need to be defined for the impact evaluation. A mixture between measurable criteria and agreed upon indicators as well as self-assessment of patients and their caregivers could be enforced. When it comes to children, special indicators need to be applied.

2.1 CASE MANAGEMENT AS A TOOL TO IMPROVE QUALITY OF LIFE

It can be argued that case management alone cannot drastically change a person’s quality of life since case management by definition is ‘the process of planning, coordinating and reviewing the care of an individual’(Hutt, Rosen, and McCauley 2004, p. 1). It should thus be considered more as a tool to help individuals cope with their life situations and help them navigate through often very fragmented systems.

In order to take the ethical considerations discussed above into careful consideration, case managers should be trained according to the needs of the participants and in supporting them exploring their needs. Following experiences from PRISMA and Esther, training of case managers need to be within a

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training course and not only on site. Establishing the role of the case manager means a serious change in professional roles, and case managers who previously worked as nurses, social workers, etc. need to identify with their new roles as case managers.

Experience from PRISMA shows that the case manager's role is well suited to assess patient's health and social care needs. Upon this single assessment, health and social care needs can and should be decided. As evidence from PRISMA shows, the power to decide upon the care one needs and wants should be upon the patient; case management can then be used as a tool to help patients get what they need and as such, case managers need to be trained accordingly.

Using the SMAF index (Hebert, Carrier, and Bilodeau 1988), an index to assess autonomy and what people need in order to (re)gain autonomy, has proven useful to assess patient's needs. A shift of focus away from disability and diseases to autonomy helped to create a common language between social care services and health care services within PRISMA.

Accordingly, training of case Managers should include (non-exhaustive list):

- Insights into the different organisations that the case managers will have to deal with (health and social care), preferably through representatives of the organisation → establishment of a network.
- Involvement of patients and care givers (what do they need?) → solution-based approach.
- Involvement of professionals → establishment of a common language.

3. THE INTERVENTION: INNOVCare's CASE MANAGEMENT APPROACH

A logic model is used as a roadmap for projects to describe the connection between actions and results. Designing a logic model is helpful to think through the process of change, which the project aims to bring about:

- identifying the problems of the target group (rare disease patients and their families);
- naming the desired results;
- developing a strategy for achieving the goals.

A logic model consists of the following elements:

- **Resources/inputs** include the human, financial and/or organisational resources which are needed to implement the project/the activities.
- **Activities** are what the project does with the resources: tools, events, workshops, actions. The activities are used to bring about the desired change.
- **Outputs** are the direct results of the project and are generally described as the number of services and actions implemented.
- **Outcomes** are specific changes in attitudes, behaviours, knowledge, skills etc. expected to results from project activities and interventions.
- **Impacts** are system level changes expected to result from project activities and interventions and/or changes in the policy arena.

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From the logic model of intervention designed by NoRo⁴, it can be summed up that the INNOVCare intervention has the following eight main objectives:

1. Increase the degree of knowledge of the disease or condition among the patient and family.
2. Increase the degree of understanding of the patient's rights among the patient and family.
3. Improve the patient's and family's communication abilities and skills of all aspects of the disease including symptoms, treatments etc.
4. Increase the degree of knowledge among the patient and their family about the services available to them.
5. Increase understanding and acceptance of the patient and his/her condition in the community.
6. Improve coordination and communication among different actors involved in the patient's treatment and care.
7. Enable the patient and their family to self-manage or self-coordinate or autonomously coordinate their treatment and care.
8. Initiate and encourage disease-related peer-to-peer learning.

To achieve these objectives, some of the activities that will be partaken include: developing an action plan with the patients and their families based on their individual needs in one of a minimum of five individual meetings between the case manager and the cases; providing information about services available to people in their conditions locally, regionally and nationally; coaching patients and their families on communication and initiation and implementation of at least two support groups for each case.

Relevant and reliable impact measurement depends on a formulated logic model that defines how inputs, incomes, concepts (objectives), processes (intervention), outputs, outcomes and impacts are connected in the context of the respective intervention. As a result the 'soft' part of both the patient and family questionnaires were developed around the eight objectives listed above (see 4.3.1.2)

ZSI together with NoRo will coordinate and monitor the compliance to the logic model (aka. fidelity).

4. METHOD OF EVALUATION

120 rare disease patients from the county of Salaj in Romania will be randomly assigned to case managers in an attempt to improve their quality of life; for nine months in two cohorts. Each patient (and for very young children and participants with cognitive difficulties – assisted) and their family will fill in a questionnaire at three points in time: at the beginning of the intervention, after nine months and after 18 months using the same measurement tools to determine whether the case management approach was able to increase their quality of life, as according to the INNOVCare project's definition of quality of life.

4.1 DESIGN

The analysis of this experiment will follow a basic two-condition repeated-measures design (Field & Hole, 2003); also known as the rotation design (Glennerster & Takavarasha, 2013) (see Figure 1). This

⁴ For the detailed INNOVCare logic model of intervention, please refer to the related document drafted by NoRo.

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design falls into the category of within-group or within-subjects designs, as all the participants will take part in all the experimental conditions (Verma, 2016). In this case, there will be two conditions corresponding to permutations of one independent variable: the experimental condition (in which participants will be assigned a case manager for nine months) and the control condition (in which participants' quality of life will still be measured, although they will not receive the services of the case manager). The independent variable has two levels: presence or absence of INNOVCare's case management. The dependent variables will be derived from a series of quality of life indicators defined by INNOVCare project's consortium together with patients and patients' representatives.

The principle behind this design is quite simple: The enrolled participants⁵ will be randomly assigned⁶ to either the treatment group (n=60) or to the control group (n=60). The participants in the treatment group (1st cohort) will then receive the intervention – in this case, INNOVCare's case management approach⁷ – for the first nine months of the pilot study. During these nine months, the participants in the control group will not receive the intervention; they will receive 'treatment as usual'. After nine months, the original treatment group will now become the control group⁸ and the original control group will now become the treatment group (2nd cohort) and receive the same intervention for the next nine months. All the participants' and their families' quality of life as according to the definition of quality of life in the INNOVCare project will be assessed at three points in time using the same measurement tools: At the beginning of the pilot study, after nine months and then at the end of the study; after 18 months.

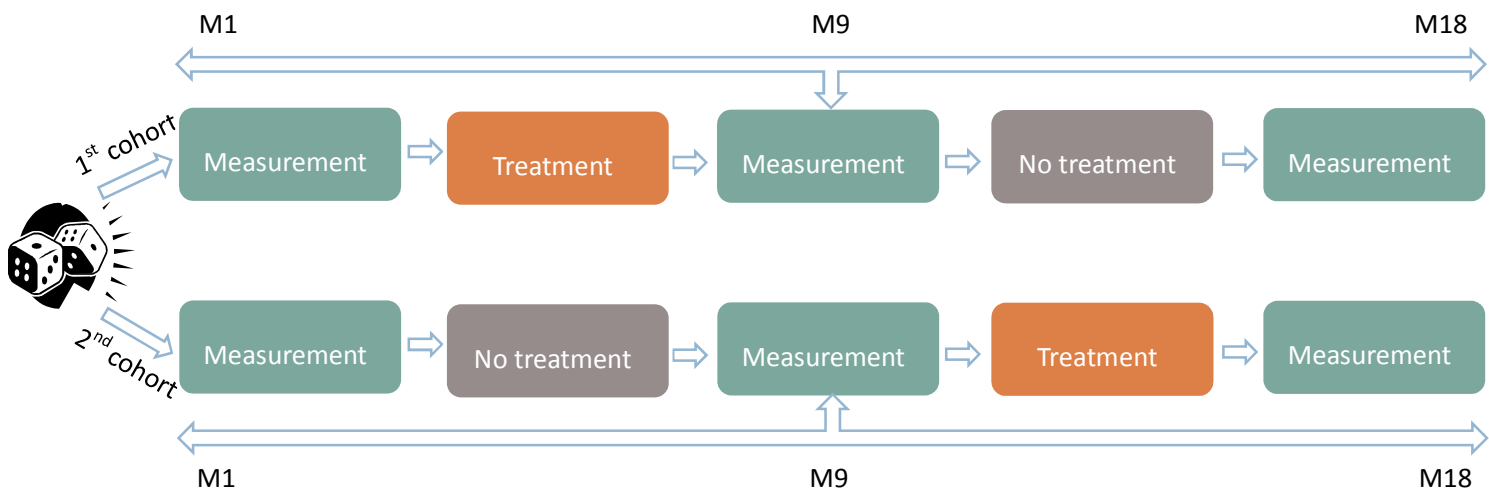


FIGURE 1: A BASIC TWO-CONDITION REPEATED-MEASURES DESIGN / ROTATION DESIGN (ADAPTED FROM (FIELD & HOLE, 2003, P. 82)

⁵ See the chapter 4.2 below on for more details

⁶ See the chapter 4.2 for the randomisation procedure

⁷ See chapter 3

⁸ Although not a 'pure' control group as described in the paragraph above

4.1.1 BENEFITS OF THE BASIC TWO-CONDITION REPEATED-MEASURES DESIGN / ROTATION DESIGN

Experiments aim to measure the effects caused by experimental manipulations. ‘True’ experiments, where the subjects are randomly assigned to different experimental conditions measure these differences reasonably well; in that they, to a large extent, manage to distinguish the true impact of the experimental manipulations from the differences caused by the mere fact that subjects are intrinsically different in their characteristics – what is often referred to as ‘noise’ (Field & Hole, 2003, p. 79) in the data or ‘extraneous variables’ (Verma, 2016, p. 3). The best way to cut out this ‘noise’ from the data is to match participants in the different experimental conditions on variables that may affect the outcome variable, thereby reducing random variability; ‘experimental error’ (Verma, 2016, p. 3). The experimental design that will be implemented in INNOVCare’s pilot study, the basic two-condition repeated-measures design / rotation design, matches participants in the two experimental conditions perfectly because all the participants will take part in all the conditions, meaning that each participant provides a perfect match for him/herself (see

Figure 2 below). In other words, ‘since each participant participates in all conditions, the only difference between a participant’s scores for the different conditions should be that produced by our experimental manipulations. Instead of participants in different groups having different ages, interests, sexes etc., all these factors are held completely constant across all conditions of the experiment, ’ (Field & Hole, 2003, p. 79). This is especially true for the second cohort which acts as the control group in the first phase of the experiment and as the treatment group in the second phase of the experiment. Due to changes that may occur despite the experiment such as getting older, overcoming or entering personal crises, progress of the disease and so on, this group can be considered only as the best possible comparison.

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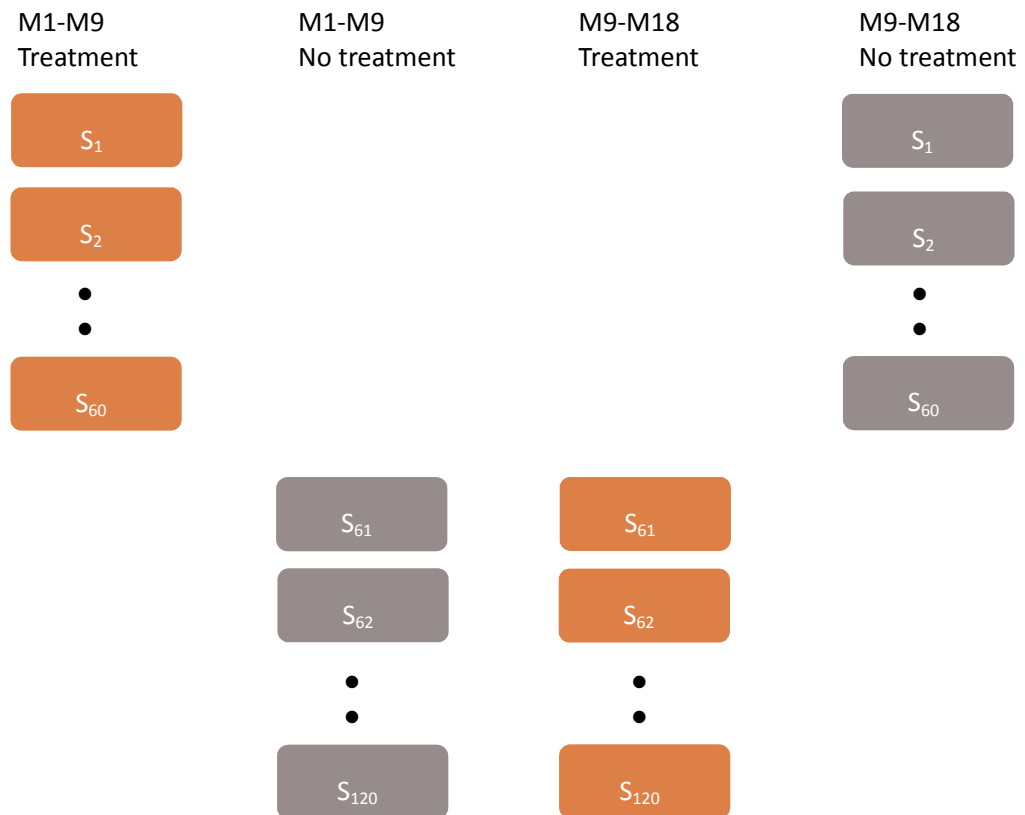


FIGURE 2: LAYOUT OF BASIC TWO-CONDITION REPEATED-MEASURES DESIGN / ROTATION DESIGN

Under limited resources and where everyone has to be ‘treated’, this design is useful as it is economical as the same participants will be used in all the experimental conditions.

4.1.2 CONSIDERATIONS OF THE BASIC TWO-CONDITION REPEATED-MEASURES DESIGN / ROTATION DESIGN

4.1.2.1 Requirement for treatment effects to be short-term

Although the main advantage of this design is the fact that each participant acts as their own control because they are involved in all the conditions of the experiment, it also poses the disadvantage that when lingering effects of the intervention exist, a group can cease to be a viable control group from the perspective of experimental ‘purity’. Therefore, there is ‘need for conditions to be reversible’ (Field & Hole, 2003, p. 82) or for the treatment effects to only be short-term and not to remain when treatment ends (Glennister & Takavarasha, 2013, p. 132). However, from the perspective of the success of the intervention it is hoped that the INNOVCare intervention will have long-term effects on the participants. As a result, it is not expected that the effects of the INNOVCare intervention will either be reversible or only exist during the period of treatment. Although this is expected to be a problem, in the case of

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INNOVCare, this problem is actually seen as a blessing. According to calculations based on the programme G*Power⁹, a minimum total sample size of 54 (n=27 per group) is required for a two-tailed dependent t-test given the probability level of p=0.05, an anticipated medium effect size (Cohen's d=0.5) (Field & Hole, 2003, p. 153) and a desired statistical power level of 0.95 (n=34 for a medium effect (d=0.5), probability level of 0.05 and a statistical power of 0.8). This means that INNOVCare's sample of n=120 (n=60 per group) is considerably higher than required for a medium sized effect n=54. As the second cohort provides a 'clean' treatment and control group comparison, the effect of the intervention can still be measured. The first cohort, which receives the intervention during the first nine months, cannot be considered a 'pure' control group in the next nine months as the effects of the intervention are expected to linger. However, monitoring the behaviour of the participants during the second phase without treatment, can give a good indication of at least the medium-term effects of the intervention which would otherwise not be possible with this kind of intervention. This may provide insight into the longer-term and indirect effects of the intervention on both the case managers and the patients.

Furthermore, this design provides the possibility of measuring the impact of the intervention in a 'between-groups' design. If only the first phase of the intervention, the first nine months of the intervention, is considered, then the two cohorts could be compared against each other in a so called 'pretest/posttest control group design'. In this case, the second cohort will still provide a 'pure' comparison group to the first cohort which will receive the intervention during that period¹⁰.

4.1.2.2 Lag between treatment and detection of effect

Although there are numerous studies in other areas that have successfully implemented a case management approach, evidence is still lacking regarding the minimum duration required for it to mature and provide impact. In this design implemented in the INNOVCare pilot study, each participant will receive the intervention for nine months. Due to lack of pre-existing evidence, there are uncertainties concerning whether nine months is long enough to change the expected outcomes. Glennerster & Takavarasha (2013, p.134) explain that the 'lag between the time of treatment and the time that the effect becomes detectable should be shorter than the treatment period' otherwise the impacts may become distorted. At the same time, when the intervention is 'too long', the effects of the intervention may become diluted or crowded out by outside factors not related to the intervention (Field & Hole, 2003). With the period of the intervention, which is certainly on the short side and owed to project-internal considerations rather than evidence on the adequacy of the intervention's dimension, there is a risk of the time limits affecting the results and possible conclusions: if positive impact can be generated within nine months, this may provide arguments for sustaining a fixed-term intervention since possible further longer-term benefits cannot be assessed. However, if a positive impact on the first cohort is not sustained in the medium term (due to the possibility of measuring medium-term impacts provided by this design), it might be an argument for policy makers to provide rare disease patients with such a service in an open-ended manner.

⁹ G*Power is a tool to compute statistical power analyses for many different t tests, F tests, χ^2 tests, z tests and some exact tests. G*Power can also be used to compute effect sizes and to display graphically the results of power analyses: <http://www.gpower.hhu.de/en.html>

¹⁰ See section 4.2.2 for more information on this possibility.

4.1.2.3 Practice effects

Each participant’s outcome will be measured at three points in time using the same data collection tools. This could therefore make the participants better practiced at filling in the post questionnaires (practice effects). The pretest in particular, could also lead to familiarity with the testing situation and could also alert the participants to the outcome of interest; leading them to filling the questionnaires not based on their ‘real’ self- assessment, but rather on what they think their expected outcome should be¹¹. This is not considered as such a problem for INNOVCare’s pilot study because the measurements are quite a long way apart (nine months). It would be unlikely that the participants’ answers would be affected by being better practiced. Riskier is the fact that each participant will be individually working with a case managers at quite an intimate level. Due to this kind of human interaction, it is understandable if participants think that the surveys are meant to judge the performance of the case managers. As a result, they might exaggerate their responses (social desirability). To avoid this, the information that will be provided to the participants will be carefully chosen¹² and a particular emphasis will be placed in explaining to the participants that the surveys are not a ‘popularity contest’ for the case managers (Aker, 2012; Field & Hole, 2003).

4.1.2.4 Anticipation effects

The design that will be implemented by INNOVCare ensures that all the participants involved in the study also receive the treatment for the same duration; the only difference is the time factor – half of the participants will receive the intervention at the beginning of the study and the rest during the second half of the study. This poses what is referred to as ‘anticipation effects’ – ‘anticipating of having, or not having treatment may change present behaviour’ (Glennerster & Takavarasha, 2013, p. 134). Participants in the first cohort may behave differently or provide inaccurate scores in the posttest because of the anticipation of the loss of treatment. Likewise those in the second cohort may behave differently in anticipation of receiving treatment. Both these kinds of situations can undermine the validity of the results.

4.1.2.5 Spillover effect

In experiments, a participant’s outcome should only depend on their own treatment status and not on the treatment status of other people around them. Spillover effects or social interaction occur for example when a participant assigned to be in the treatment group shares what he or she has learned through his or her treatment status with a person in the control group of the study. This occurs through ‘physical contact, behavioural (e.g. imitating change of behaviour of someone in the treatment group), informational, marketwide or general equilibrium (Glennerster & Takavarasha, 2013, p. 113). This may affect the outcomes of the participants in the control group as through this, they will indirectly be affected by the treatment. In order to have a ‘clean’ impact evaluation, it is necessary that the control group is not affected by the changes of the participants in the treatment group as a result of the

¹¹ See section 4.3.1.2.2 on more information on practice effects and other limitations of self-assessment questionnaires.

¹² See section 4.4.3 for more information on the information that will be provided to the participants.

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intervention. Most of the existing patients at NoRo know each other quite well because they already take part in different group activities together or the parents/caregivers spontaneously socialise while waiting for the children to finish therapies at NoRo Center. Due to randomisation, it might be the case that the existing patients are split into the first and second cohort. As it is impossible to control the kind of interactions the participants have among themselves, the evaluation will control for spillover effects (which again, would be desirable from the point of view of the intervention) by including this as part of the self-assessment questionnaires (pre, post, post-post). If this variable is not significant, the analysis of the results will then assume a ‘no interference assumption’ or ‘stable unit treatment value assumption’ (SUTVA) which makes the assumption that subjects are only affected by their own treatment status (Morgan & Li, 2014). However, if the spillover variable is significant, the analysis will adjust for spillovers (Glennerster & Takavarasha, 2013, pp. 354-355).

4.2 PARTICIPANTS

Participants¹³ are rare/complex disease patients and their families living in the county of Salaj in Romania. The NoRo Resource Centre, which is one of the partner organisations of the INNOVCare project, currently caters for 60 rare/complex disease patients; 50 children (1 under 3 years, 17 between 3-6 years, 27 between 7-14 years, 5 between 15-18 of which 28 are male and 22 are female) and 10 adults (3 between 18-24 years, 6 between 25-35 years, 1 older than 35 of which 9 are female and 1 is male). It would be considered unethical to deny any of these existing patients the opportunity to access the services of INNOVCare’s case managers and thereby possibly benefitting from them, not only because they are considered a vulnerable target group, but also because case management as an approach has been tried and tested in many other different fields for example education and ageing and can be widely considered as beneficial¹⁴.

Due to the fact that the existing patients of NoRo are quite selected, in that the centre intentionally provides its services mainly to children affected by rare diseases and different strains of autism, this sample lacks external validity. External validity is ‘the extent of generalizability of research findings to the population from which the sample is derived. To ensure external validity, it is important that the sample is randomly drawn from the population of interest (Verma, 2016, p. 13).’ As it cannot be said that NoRo’s existing patients represent the general population of rare disease patients, even just in the county of Salaj, because they have not been randomly drawn from the general population of interest, it was considered important and necessary to additionally recruit new participants, who are not currently under NoRo’s care. 60 new rare disease patients from the county of Salaj will be recruited by NoRo to take part in the experiment. This will follow a random stratified technique which tends to increase

¹³ Every mention of ‘participant(s)’ in this report refers not only to the rare disease patients, but also to their families.

¹⁴ Some projects that have successfully implemented a case management approach include:

1. Esther: patient-centred approach to health and social care for elderly, including case management. It was successfully piloted in a region in Sweden from which it spread out globally - <http://plus.rjl.se/infopage.jsf?nodeId=31383> (Gruber & Holtgrewe, 2016, p. 7)
2. Community of matrons: Community Matrons act as a central contact point for patients with complex and multiple conditions - <http://www.nuffieldtrust.org.uk/node/463> (Gruber & Holtgrewe, 2016, p. 8)
3. PRISMA: is a model successfully tested in Québec, Canada. It involved, among others, coordination between stakeholders, case management, single entry point, individualized service plan and shared information systems - <http://www.cnsa.fr/parcours-de-vie/maia> (Gruber & Holtgrewe, 2016, p. 14)

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representativeness of the population and allows for analysis on sub-group level based on the variables used for the stratification¹⁵.

Although with the recruitment of the new patients it is aimed to increase external validity, it should be noted that this will only be true to a degree as in the county of Salaj there is a database of all the rare disease patients. There are currently 210 rare disease patients in the database, deducting the 60 existing patients of NoRo, only 150 rare disease patients are left from which 60 will additionally be selected - this represents about 40% of the remaining eligible population. The total sample size of 120 represents an overwhelming 57% of the total eligible population (see **FIGURE 3**).

Despite the fact that sampling 60 new patients at random increases the ability to infer the results of the pilot study to the general population of rare disease patients at least in the county of Salaj and also because the increased sample size increases the statistical power of the findings ('findings based on larger samples have more certainty than those based on smaller ones' (Kumar, 2005, p. 168)), this move presents an additional ethical concern of leaving the remaining 90 rare disease patients completely out of the study¹⁶.

NoRo's existing services are very similar to the intervention that will be implemented in INNOVCare and could be considered superior to some extent. As half of the participants already benefit from NoRo's services, it may prove difficult to detect the exact impact of the new intervention within this group. This speaks for sampling new participants (n=60) who do not already benefit from NoRo's care because it increases the likelihood of the model detecting the true impact of the intervention.

¹⁵ See chapter 4.2.1 for more details on the stratification process

¹⁶ See chapter 4.5 for more information on the ethical concerns affecting this study and how these have been taken into consideration).

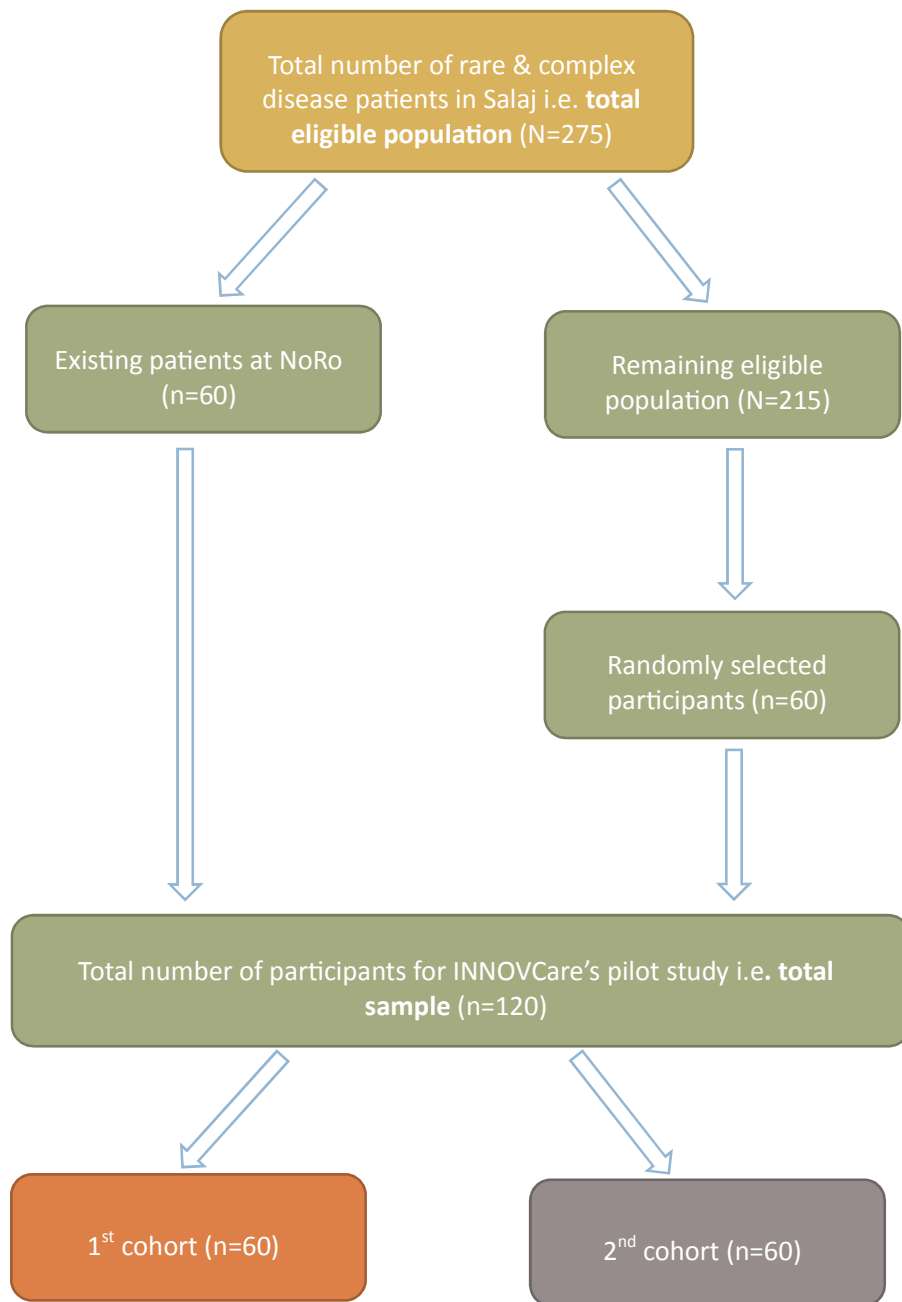


FIGURE 3: TOTAL ELIGIBLE POPULATION AND TOTAL SAMPLE FOR THE INNOVCARE PILOT STUDY

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Participation in the experiment is on a voluntary basis; the participants will not be remunerated or compensated in any form. Each participant and for children their parents, will be required to sign an informed consent form¹⁷ agreeing to take part in the activities of the pilot study.

4.2.1 RANDOM SAMPLING

‘Sampling is the process of selecting a few from a bigger group to become the basis of estimating or predicting the prevalence of an unknown piece of information, situation or outcome regarding the bigger group (Kumar, 2005, p. 164)’ – the process of choosing research participants from the population. Random or probability designs are based on the idea that ‘each element in the population has an equal and independent chance of selection in the sample’ (Kumar, 2005, p. 168). In the case of INNOVCare’s pilot study, ‘an element’ refers to individual rare disease patients in the county of Salaj. This is because the intervention is implemented at individual level.

It could be argued that both random and non-random sampling methods are involved in INNOVCare’s pilot study. The automatic inclusion of the existing patients of NoRo in the study presents the non-random aspect. Removing this group of patients from the total eligible population leaves 215 rare disease patients in the county of Salaj who have an equal and independent chance of being selected for the study – following the definition of random/probability sampling; this presents the random sampling aspect of the INNOVCare pilot study. Random sampling enables generalisation of findings to the population from which the sample has been drawn (Verma, 2016).

There are three types of random/probability sampling: simple random sampling, stratified random sampling (proportionate and disproportionate) and cluster sampling. For the purpose of this study, a stratified random sampling will be used to select 60 participants, who are rare disease patients in the county of Salaj currently not benefitting from NoRo’s services. This method is superior to both the simple random sampling and the cluster sampling because stratified random sampling more accurately represents the whole population.

The remaining eligible population, after eliminating those who are currently under NoRo’s care (n=215), will be divided into different groups also known as strata based on their characteristics and on characteristics which are likely to affect or be related to the outcome or dependent variable of the experiment. Considering that the majority of the existing patients at NoRo are under 18, age will be one of the variables for stratification to ensure that the other age groups are also represented. Sampling other age groups also increases validity in the data because due to ‘maturation’ participants especially ‘young ones may change simply as a consequence of development; changes of which might be confused as those due to the manipulations of the independent variable’ (Field & Hole, 2003, p. 59).

Depending on the ease of access to the following indicators, some of these will be included in the stratification too: type of rare disease, degree of disability, existence of treatment and main care giver. As one of the advantages of stratification is the possibility of sub-group analysis of data, a good balance of stratification variables should be struck to ensure that the groups generated are not too small rendering sub-group analysis meaningless. Once the eligible sample has been divided into groups, the sample is selected proportionally to the size of each stratum in the eligible population – this is referred

¹⁷ See section 4.4.3 for more details on the consent form

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to as 'proportionate stratified sampling' (Kumar, 2005, p. 176) (see Figure 4 for an example of this sampling method).

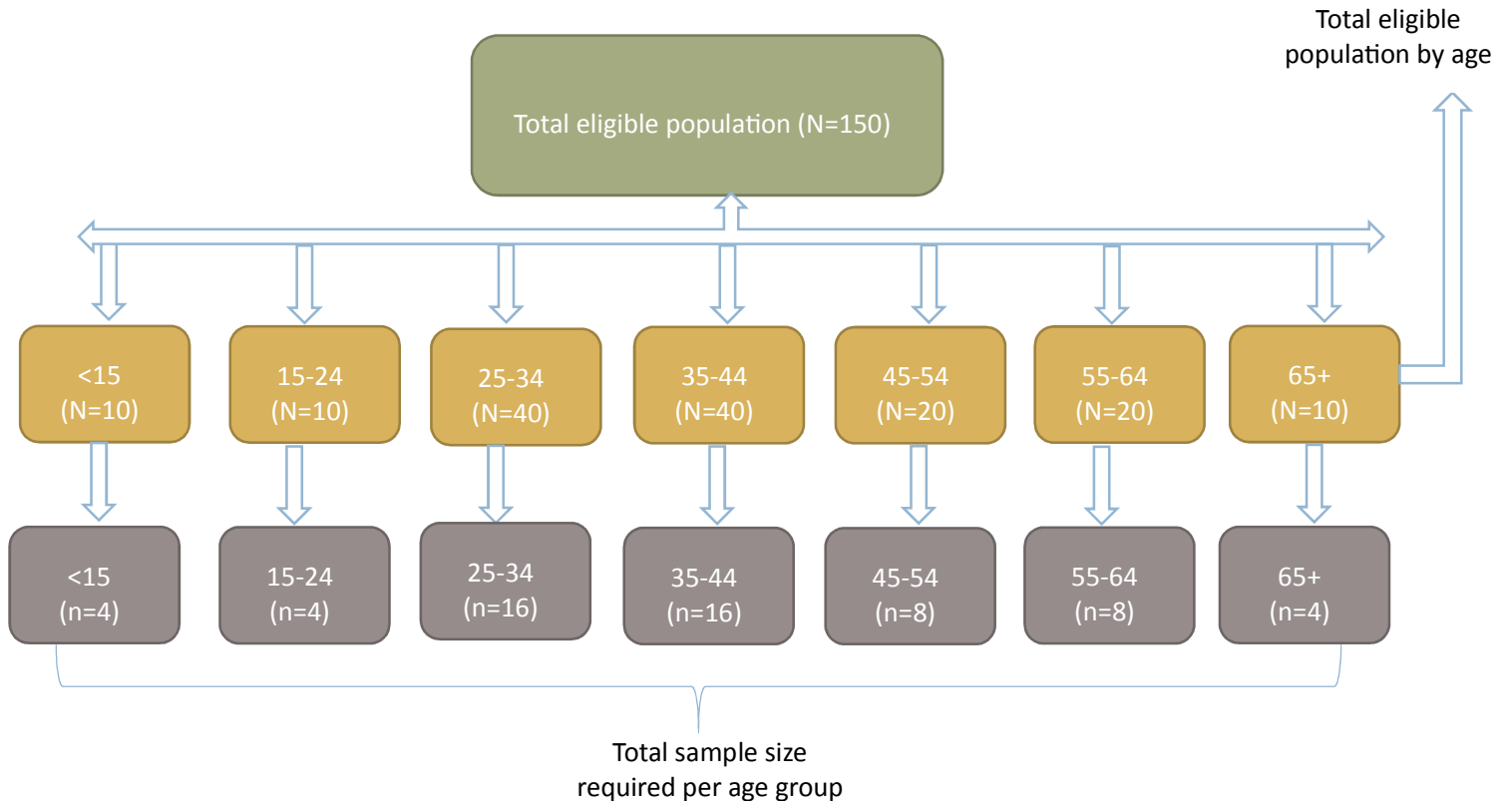


FIGURE 4: EXAMPLE OF A PROPORTIONATE STRATIFIED SAMPLING WITH A TOTAL POPULATION OF 150 AND A REQUIRED TOTAL SAMPLE SIZE OF 60 WITH STRATA BASED ON A SINGLE CHARACTERISTIC: AGE

Figure 5 below is a visualisation of the actual strata used for the INNOVCare pilot study.

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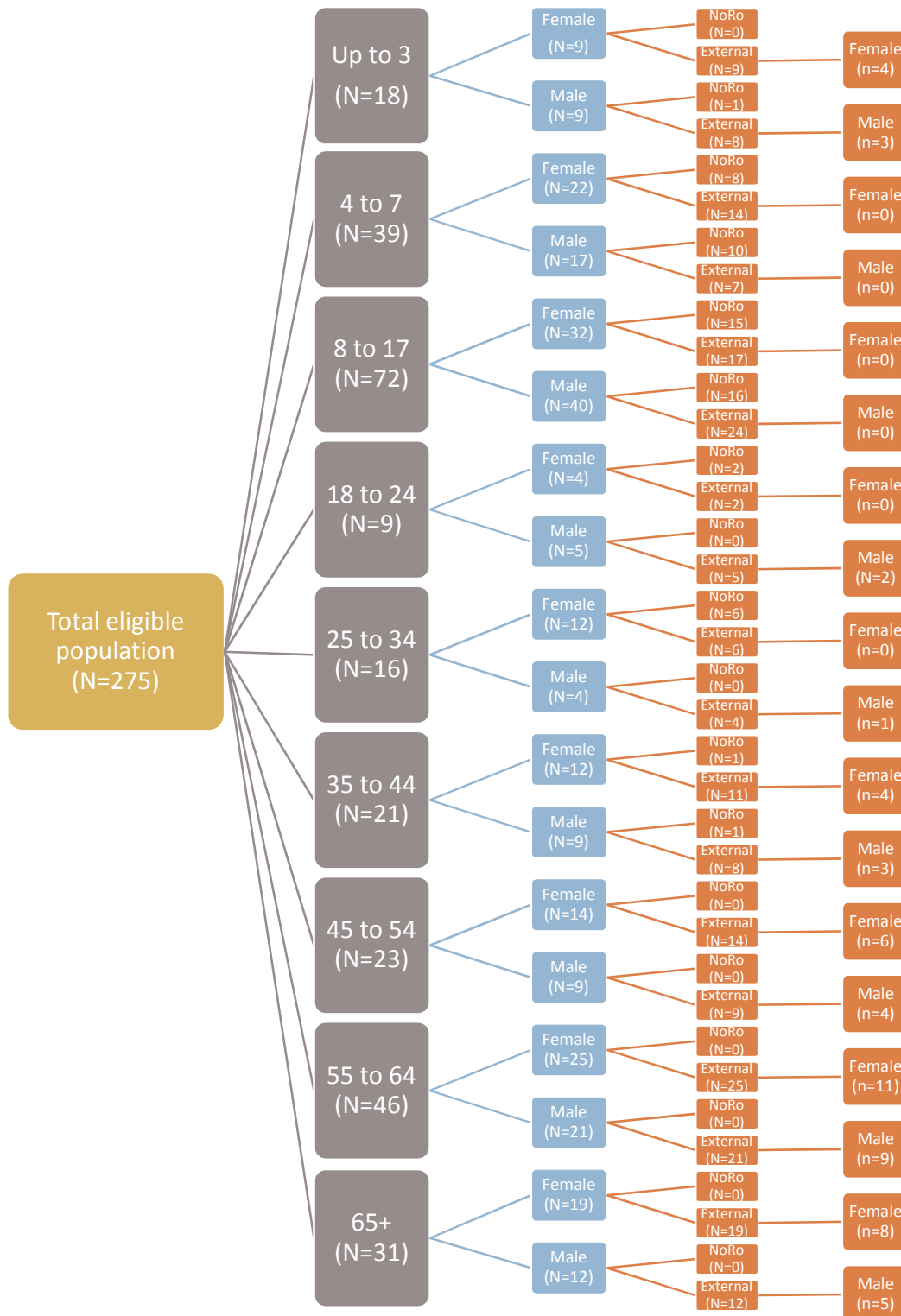


FIGURE 5: DEPICTION OF THE SAMPLING PROCEDURE OF INNOVCARE

The random sampling will ideally be carried out by ZSI, the partner organisation in INNOVCare responsible for the evaluation of the pilot study. This however depends on permission to access data of the whole population of rare disease patients in the intervention site. Failing this, NoRo, the organisation responsible for the implementation of the pilot study, which already has access to the database, will carry out the random sampling with the support of ZSI¹⁸.

4.2.2 RANDOM ASSIGNMENT OF THE PARTICIPANTS INTO THE TWO EXPERIMENTAL CONDITIONS

Randomisation is considered the ‘golden standard’ of experimental designs because it reduces the ‘plausibility of alternative explanations for observed effects’ (Shadish, et al., 2002, p. 247). The objective of randomisation is to ‘ensure that that the only systematic difference between the programme participants (treatment) and non-participants (control) is the presence of the programme’ (Aker, 2012, p. 6). This in essence means randomly assigning the participants to the experimental conditions; in INNOVCare’s case, to the 1st cohort and to the 2nd cohort. Like in random sampling, here also each participant has an equal chance of being placed into any group. By the virtue that everyone recruited in the experiment will need to receive treatment because INNOVCare considers it unethical to withhold treatment from one group, randomisation here means that participants will randomly be assigned a time when they can access treatment: the first cohort will receive treatment during the first nine months while the second cohort will receive treatment during the following nine months of the pilot study (Glennerster & Takavarasha, 2013).

Like in random sampling, the process of randomly allocating treatment to subjects can also take a number of shapes. The idea of randomisation is to ensure similarity in the different groups in the experiment, hence controlling selection bias and ‘extraneous variables which might affect the findings of the study’ (Verma, 2016, p. 3). Homogenous groups resulting from random allocation of treatment ensure internal validity – ‘the extent to which one can say that the variation observed in the dependent variable is due to the variation in the independent variable’ (Verma, 2016, p. 13).

In chapter 0 the advantage that each participant in the basic two-condition repeated-measures design / rotation design provides his or her own comparison, because each participant takes part in both experimental conditions, has been particularly highlighted. Considering only this, it could be argued that simple random assignment into the treatment and control group would be sufficient for this case. The most common procedure for simple random sampling is the coin toss where on any given toss there is a 50% chance of landing on heads or tails (see Figure 6 for an example).

¹⁸ Please refer to the ‘Technical note on random sampling and random allocation’ for the detailed sampling process

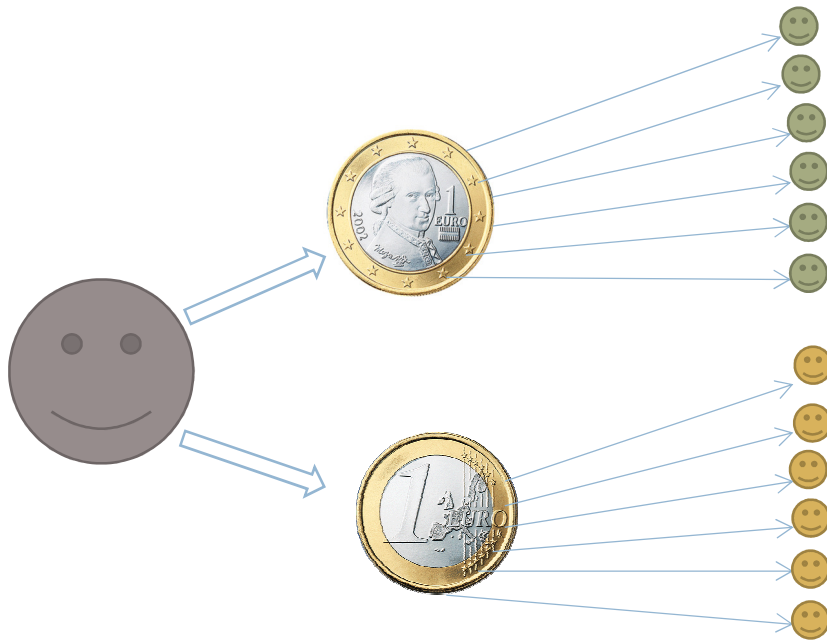


FIGURE 6: ILLUSTRATION OF A COIN TOSS (50:50) BASED ON (KEUSCHNIGG & WOLBRING, 2015, P. 164)

However, as explained also in chapter 0, because of lingering effects, the first cohort, those exposed to the intervention during the first phase of the intervention, cannot provide a ‘pure’ comparison group for itself. In order to be able to still counterfactually measure the impact of the intervention on this group, the randomisation will have to be done in a way that, although the control group (the second cohort) will not be a perfect match to the experimental group (first cohort) during the first nine months of the intervention because they are not the same participants, the two groups have to be as similar as possible. Simple random assignment does not control for characteristics of the participants that could affect the outcome variable and can therefore suffer from ‘chance bias’; which is where the resulting groups are not balanced on important covariates or groups that are not evenly balanced. This is more so a problem for smaller samples of which INNOVCare falls into this category. The best way to solve this problem is using matched-pair or stratified random assignment.

In matched-paired random assignment, units are matched on a list of important variables or even just one continuous variable. Each resulting unit in the pair is then randomly assigned to either the treatment group or to the control group (Glennister & Takavarasha, 2013).

Participants in the sample	Grade point average in %
S ₁	49%
S ₂	89%
S ₃	67%
S ₄	85%
S ₅	23%
S ₆	36%
S ₇	12%
S ₈	55%
S ₉	63%
S ₁₀	36%

TABLE 2: ILLUSTRATION OF MATCHED-PAIRS DESIGN

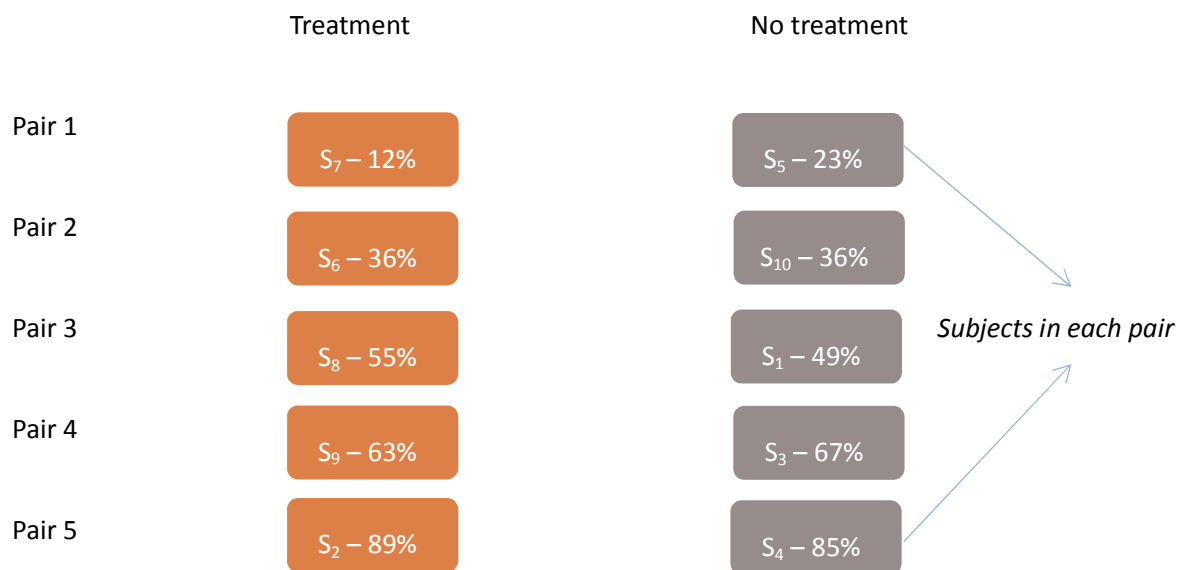


FIGURE 7: ILLUSTRATION OF MATCHED-PAIRS DESIGN. ADAPTED FROM (VERMA, 2016, P. 8)

It was initially thought of performing a matched-pair randomisation procedure to assign the participants to the two experimental conditions in INNOVCare’s pilot study, however in this case the limitations of such a randomisation design outweighed its benefits. Although this design has the advantage that it can control for multiple extraneous variables (through the matching variables), it can also be rendered unrewarding if the matching variables are not related to the outcome variable. For

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example if one is looking at the effectiveness of exercise, it would be rather meaningless to match the participants based on their IQ as this variable is unlikely to affect the outcome (example drawn from Verma, 2016, p. 8). Due to the complexity of topic under investigation in the INNOVCare pilot study, namely quality of life of rare disease patients; it would be very difficult to come up with matching variables from which the matching could be based. A good option would be to base the matching on the results of the pretest. Another reason, and in this case the main reason, for rejecting matched-pairing for this particular study is the argument presented by Glennerster & Takavarasha (2013). They argue that because in matched-paired randomisation, when one unit for whatever reason drops out of the study, then the matched unit in the pair also has to be removed from the analysis, which is basically reacting to the effects of the intervention (which one shouldn't do as the aim is to measure the effects of the intervention; positive or negative) and also interferes with the randomisation thus nullifying it.

'In paired matching, if we lose one unit in the pair, essentially we have to drop the other unit from the analysis. That is because the other unit does not have a comparison. Some evaluators have mistakenly seen this as an advantage of pairing: they suggest that if one person drops out of the study, we can drop their pair and not worry about attrition. But in fact we drop the pair we have just introduced even more attrition bias. This is not a good approach because we are dropping units in response to their actions and behaviours. We have to stick to initial randomization; changing what we do based on any action after this point undoes randomisation. Our suggestion is that if there is a risk of attrition (for example of the randomization and pairing are at the individual level), use strata that have at least four units rather than pairwise randomization (strata with two units) (Glennerster & Takavarasha, 2013, p. 159).'

All things considered, the randomisation in the INNOVCare pilot study, like suggested in the quote above, will implement a stratified random assignment technique; also commonly referred to as a 'randomised block design' (Verma, 2016, p. 6). This design produces balance, increases statistical power and enables sub-group analysis (Glennerster & Takavarasha, 2013, p. 154). Like in stratified random sampling, the total sample (n=120) will be divided into blocks or groups based on variables that are likely to affect the outcome of the experiment. Some of the variables under consideration, like in the stratified sampling, include: type of rare disease, degree of disability, existence of treatment and main care giver. The results of the pretest (baseline value of the outcome of interest) are also likely to be used as a variable for the randomisation process. Exactly which variables will be used, will highly depend on the kind of data from the sample that is readily available. The variables most correlated to the outcome of interest will be prioritised (in the first instance; the baseline value). To enable sub-group analysis, gender and age will also be included as blocking variables. As age is a continuous variable, appropriate groupings of the variable will be considered to yield suitable strata. Each strata or block should be divisible by the randomisation cell; in INNOVCare's pilot study this signifies two (experimental and control group). Glennerster & Takavarasha (2013) suggest that if there is risk of attrition, loss of subjects during the experiment, each stratum should include at least twice the number of randomisation cells. In INNOVCare, this is definitely a problem that could be encountered, and as a result, the minimum number of participants in each block is set to four. In this process, the fact that the higher the number of stratification variables used, the more difficult it can be to strike balance, will be taken into consideration.

For example considering just four blocking variables: gender (two levels: females and males), age (three levels: up to and including 17, 18-64 and 65+), existence of treatment (two levels: treatment or no treatment) and self-assessment of quality of life (three levels: poor, fair, good), 36 strata are formed suggesting less than four participants per stratum. As it is not expected that each stratum will be equal

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in size, a preliminary blocking with these variables will be attempted. Should any stratum have less than four participants, either one of the blocking variables could be removed altogether or the levels of some of the blocking variables e.g. age and quality of life could be reduced by one level. As a result, INNOVCare's block randomisation could look like Figure 8 below.

ZSI, the partner organisation in INNOVCare responsible for the evaluation of the pilot study will perform the randomisation. To ensure that the data is handled anonymously, NoRo, the project partner responsible for the implementation of the intervention, will anonymise the data of the selected sample. This means that each participant will be given a code and any analysis of the data will use only data which has been coded. NoRo will need to keep a record of the codes and the names of the participant to ensure that the right participants receive the treatment at the right time and the pretests and posttests for each participant can be linked. The randomisation process will be carried out as follows:

1. Based on the available variables of the selected participants, some of the variables will be used as blocking variables to divide the sample into strata.
2. Each stratum will be saved into an individual spreadsheet document.
3. Using the statistics software SPSS and each stratum at a time, each participant in the stratum will be assigned a random number between 1 and 1000 ((this reduces the chances of duplication of the random numbers): SPSS command RV.UNIFORM (1,1000) – this is a process of simple random assignment.
4. The cases in each stratum will then be sorted in ascending order of the random numbers (smallest to largest)
5. The first half of the cases will then be assigned to the experiment group and therefore in the first cohort to receive the treatment during the first nine months of the experiment, while the second group will be assigned to the control group and therefore in the second cohort to receive treatment in the second half of the experiment.
6. An ex-post assessment of the randomisation procedure will then be carried out. For gender and existence of treatment, the mean and the Lamda test will be carried out. For the age and self-assessment of quality of life, a test for the mean and t-tests will be carried out. Depending on what other patient data can be accessed, these two will be controlled in the ex-post assessment to ensure that the two groups are as balanced as possible. These results will be saved in a file: 'Technical note: ex post assignment randomisation'.
7. The steps for randomisation 6 to 9 above are repeated for all the strata.
8. After all the participants in all the strata are assigned to either the treatment group or the control group, the files will then be merged to have one file with 120 cases 60 of which are assigned to the treatment group (first cohort) and the other 60 in the control group (second cohort).
9. This list is then shared with the colleagues at NoRo so that the activities of the pilot study can start.¹⁹

¹⁹ Please refer to the 'Technical note on random sampling and random allocation' for the detailed random allocation process

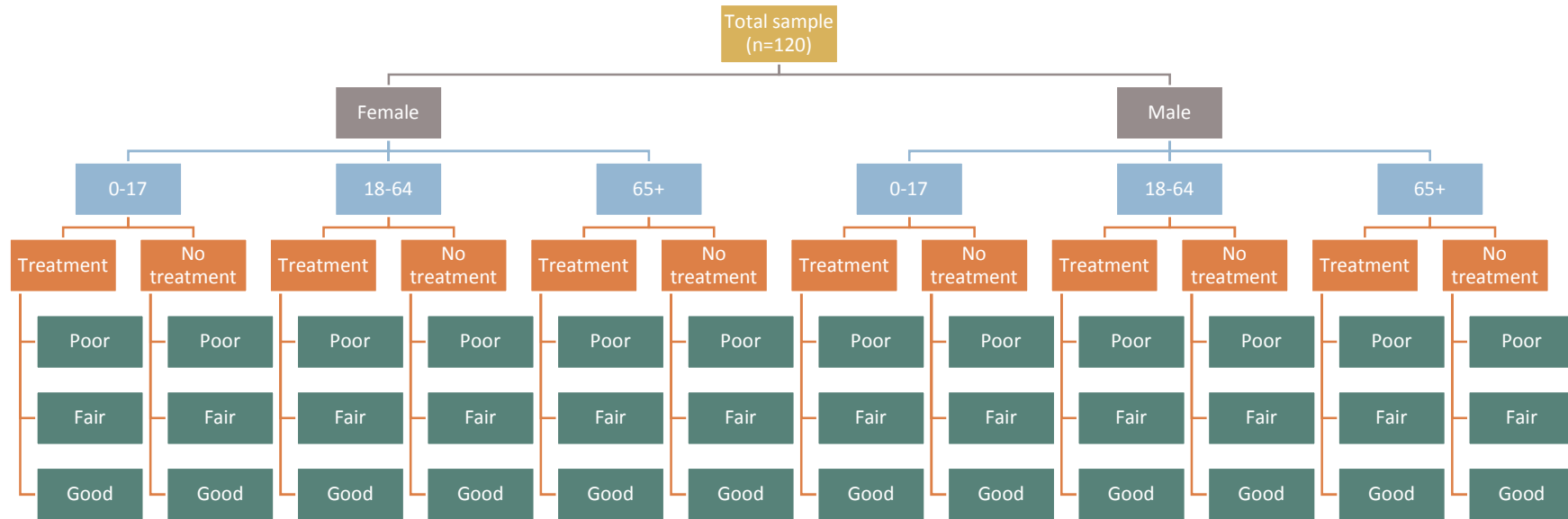


FIGURE 8: ILLUSTRATION OF HOW THE RANDOMISED BLOCK DESIGN FOR INNOVCARE COULD LOOK LIKE WITH THE FOLLOWING BLOCKING VARIABLES: GENDER, AGE, EXISTENCE OF TREATMENT, ASSESSMENT OF QUALITY OF LIFE AS ACCORDING TO THE PRETEST

4.3 APPARATUS

This section of this report presents the instruments that will be used to measure the quality and effectiveness of INNOVCare’s pilot study. The evaluation model of this study involves both summative and formative evaluation²⁰.

Impact evaluation, which falls under the category of summative evaluation, assesses the effect of an intervention on the target group. In this context, the impact evaluation refers to the examination of whether the INNOVCare’s case management approach has had an effect on the quality of life of rare disease patients. In this case, the impact evaluation is done using data collected using the ‘questionnaire on hard facts’ (‘hard questionnaire’), pretest, and posttests scores (‘soft questionnaire’).

On the other hand, the aim of formative evaluation is ‘to validate or ensure that the goals of the instruction are being achieved and to improve the instruction, if necessary, by means of identification and subsequent remediation of problematic aspects’ (Weston, et al., 1995, p. 30). In the case of INNOVCare’s pilot study, relevant data collection instruments (see section 4.3.2) will serve the purpose of ensuring that the activities of the intervention are being correctly implemented in compliance with the logic model and where there are hitches, possible solutions can be quickly found. These tools are specifically useful for the INNOVCare intervention because:

- As the intervention will be implemented in 2 cohorts, standardisation in the delivery of the treatment is aimed to allow comparison. However, slight differences may still occur for example due to learning effects of the case managers and it is hoped that through these tools, such differences can be documented.
- As the participants are at the centre of the study, should any wishes for improvement of the intervention be expressed after the first phase, through consultations with colleagues at NoRo and with the whole consortium, these changes could be implemented for the second cohort. As a result, it is important that if such wishes exist, the participants find a platform to express them. These could possibly be done using some form of qualitative data collection instruments.

For the purpose of the INNOVCare project, the data collected using the impact evaluation tools will be quantitatively analysed using different statistical techniques (see chapter 5). The formative evaluation, which is mainly qualitative, will be briefly descriptively analysed as their main purpose is providing background and context information regarding the process of the experiment.

4.3.1 QUANTITATIVE DATA COLLECTION INSTRUMENTS FOR THE SOCIAL & ECONOMIC IMPACT EVALUATION

The data collection instruments designed for the social and economic analysis of INNOVCare pilot study can broadly be classified into two main questionnaires: the patient questionnaire and the family questionnaire. These two main questionnaires include some original questions from the researchers involved, some individual questions from different existing instruments and some validated instruments

²⁰ Impact evaluation falls under the category of summative evaluation. To clarify the difference between summative and formative evaluation, Robert Stake, professor Emeritus of Education at the University of Illinois as cited in Shute, V., J. and Becker, B. J. (2010) says: ‘When the cook tastes the soup, that’s formative; when the guests taste the soup, that’s summative (Shute & Becker, 2010, p. 7).’

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in their entirety for example the EQ-5D-Y, EQ-5D-5L, the Zarit Caregiver Burden Interview and the DISABKIDS questionnaires (SMILEY & DCGM-12).

The term ‘broadly’ has been deliberately used in the paragraph above because the degree to which the questionnaires can be completed highly depends on the patient’s age, cognitive abilities and existence of family support. **Fehler! Verweisquelle konnte nicht gefunden werden.** below shows each part of the questionnaire and the intended target group.

Patient questionnaire					Family questionnaire
DISABKIDS SMILEY	DCGM-12	EQ-5D-Y	‘Soft’ items [Q3 – Q49 & Q71 & Q72]	‘Hard’ items [Q50 – Q70]	
<ul style="list-style-type: none"> ▪ Patients <u>4 to 7 years old</u> ▪ Older patient with serious cognitive difficulties 	<ul style="list-style-type: none"> ▪ Patients <u>8 years and older</u> 	<ul style="list-style-type: none"> ▪ Patients <u>8 years and older</u> 	<ul style="list-style-type: none"> ▪ Patients <u>8 years and older</u> 	<ul style="list-style-type: none"> ▪ Adult patients, living alone and managing their own care 	<ul style="list-style-type: none"> ▪ Family members most closely involved or informed about the care of patients selected to take part

TABLE 3: OVERVIEW OF THE DIFFERENT DATA COLLECTION INSTRUMENTS AND THE TARGET GROUP

4.3.1.1 Patient questionnaire

As depicted in **Fehler! Verweisquelle konnte nicht gefunden werden.** above, the full patient questionnaire consists of the following dimensions:

1. Health-related quality of life (HRQoL) measured by:
 - a. DISABKIDS-SMILEY (self-reported)
 - b. DCGM-12 (self-reported)
 - c. EQ-5D-Y (self-reported)

2. ‘Soft’ items [Q3 – Q49 & Q71 & Q72] :
 - a. Knowledge of condition
 - b. Knowledge of rights as patients
 - c. Communication skills regarding condition, treatment and care
 - d. Knowledge of available services
 - e. Understanding and acceptance in the community
 - f. Coordination of care
 - g. Support from peers
 - h. Changes within the family

3. ‘Hard’ items [Q50 – Q70]:
 - a. Living situation
 - b. Educational background

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- c. Employment status
- d. Ethnicity
- e. Use of healthcare resources
- f. Use of community and other services
- g. Health insurance and cost-sharing
- h. Household composition and income

As described in **Fehler! Verweisquelle konnte nicht gefunden werden.** above, the whole patient questionnaire cannot and should not be filled in by all the patients. As a result, the dimensions are compiled in different ways to suit the different target groups (according to age and situation of patient). Below is a list of the different versions of the patient questionnaires and their target groups:

Name of questionnaire	Components	Target group
Patient-SMILEY	DISABKIDS – SMILEY (self-reported)	<ul style="list-style-type: none"> ▪ Patients aged 4 to 7 ▪ Patients older than 7 with serious cognitive difficulties
Patient-8+	<ul style="list-style-type: none"> ▪ DCGM-12 (self-reported) ▪ EQ-5D-Y (self-reported) ▪ ‘Soft’ items 	<ul style="list-style-type: none"> ▪ Patients aged 8 and above
Patient-SOLO	<ul style="list-style-type: none"> ▪ DCGM-12 (self-reported) ▪ EQ-5D-Y (self-reported) ▪ ‘Soft’ items ▪ ‘Hard’ items 	<ul style="list-style-type: none"> ▪ Adult patients, living alone and managing their own care

TABLE 4: THE DIFFERENT VERSIONS OF THE PATIENT QUESTIONNAIRE, THEIR COMPONENTS AND TARGET GROUPS

Following the evaluation design of the study, the same questionnaire will be administered at three points in time. Each of the 120 participants of the INNOVCare pilot study and their families will be requested to complete the questionnaires at the three points in time regardless of which cohort they fall into. Each of the three questionnaires listed in **Fehler! Verweisquelle konnte nicht gefunden werden.** above has a PRE and a POST version. The PRE questionnaire has fewer items than the POST questionnaire, because it omits items directly related to the case management service being offered. As the different cohorts receive the intervention at different points in time, special care need to be taken when preparing the questionnaires for administration. **Fehler! Verweisquelle konnte nicht gefunden werden.** below shows which cohort receives which questionnaire at which point in time.

	1 st Measurement (March 2017)	2 nd Measurement (November 2017)	3 rd Measurement (July 2018)
1 st cohort	PRE Patient-SMILEY	POST Patient-SMILEY	POST Patient-SMILEY
	PRE Patient-8+	POST Patient-8+	POST Patient-8+
	PRE Patient-SOLO	POST Patient-SOLO	POST Patient-SOLO
	PRE Family questionnaire	POST Family questionnaire	POST Family questionnaire
2 nd cohort	PRE Patient-SMILEY	PRE Patient-SMILEY	POST Patient-SMILEY
	PRE Patient-8+	PRE Patient-8+	POST Patient-8+
	PRE Patient-SOLO	PRE Patient-SOLO	POST Patient-SOLO
	PRE Family questionnaire	PRE Family questionnaire	POST Family questionnaire

TABLE 5: PRE OR POST VERSIONS OF THE QUESTIONNAIRES ACCORDING TO COHORT AND MEASUREMENT TIME

4.3.1.2 Family questionnaire

The family questionnaire is built very similarly to the patient questionnaire with the exception that it does not include the instruments measuring the health-related quality of life (HRQoL) of patients for example the DISABKIDS questionnaires and the EQ-5D-Y and that it includes information on the family member filling in the questionnaire as well as his/her own HRQoL including EQ-5D-5L and Zarit Burden Interview- 12 items. It comprises of the following dimensions:

1. ‘Soft’ items [Q1 – Q50 & Q76 - Q78] :
 - a. Knowledge of the condition of the person they care for
 - b. Knowledge of the rights of the person they care for
 - c. Communication skills regarding condition, treatment and care of the person they care for
 - d. Knowledge of available services for the person they care for
 - e. Understanding and acceptance in the community of the person they care for
 - f. Coordination of care of the person they care for
 - g. Support from peers
 - h. Current health and well-being of the family member (Zarit Burden Interview and EQ-5D-5L)
 - i. Changes within the family

2. ‘Hard’ items [Q51 – Q75]:
 - a. Living situation of the person they care for
 - b. Education of the person they care for
 - c. Employment status of the person they care for
 - d. Ethnicity of the person they care for
 - e. Use of healthcare resources related to the condition of the person they care for
 - f. Use of community and other services related to the condition of the person they care for

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- g. Health insurance and cost-sharing related to the condition of the person they care for
- h. Household composition and income
- i. Family member's own:
 - i. Living situation
 - ii. Educational background
 - iii. Ethnicity
 - iv. Employment status

The target group for this questionnaire are family members of the patients selected to participate in this study:

1. If the patient has a personal assistant and this is one of his/her relatives, then this person should complete this questionnaire.
2. If the patient has a personal assistant but this person is not a relative, then the relative most closely involved or informed about the patient's care should complete this questionnaire (for example: parents, spouses, children etc.).
3. If the patient does not have a personal assistant, then the relative most closely involved in the patient's care should complete the questionnaire.
4. If the patient lives alone and is his or her own main caregiver, then the patient should complete the 'Patient-SOLO' questionnaire. In this case, no family member would complete the family questionnaire.

4.3.1.2.1 PRETESTING

To determine the effectiveness, the strengths and weaknesses of the questionnaires, a survey pretest will be performed. The aim is to have a reliable question format and a good wording and order.

Altogether cognitive pretests (comprehension probing) (Prüfer & Rexroth, 2005) with a minimum of three participants will be performed. Cognitive pretesting is a well-known method to collect verbal information regarding survey responses and to evaluate whether the question is measuring the construct the researcher intends to measure. The results from pretesting are then used to adjust problematic questions in the questionnaire before fielding the survey instrument to the full sample.

This method includes the following techniques:

- **Probing:** When applying probing techniques, the interviewer reads out the survey question and the respondent answers. Afterwards, the interviewer 'probes' further into the basis for the response. This means that the interviewer asks for specific information relevant to the question or to the specific answer given.
The interviewer can either ask the respondent what a particular term means to him or her (comprehension probing) or ask the respondent various probing questions including how he/she arrived at an answer or how difficult the question was, what she/her thinks about the question.
- **Confidence Rating:** the interviewer asks the respondent how sure her/she is about his/her answer
- **Paraphrasing:** the interviewer asks the respondent to repeat the question in his/her own words.
- **Thinking aloud:** For this technique interview respondents are instructed to 'think aloud' as they answer the survey question. The interviewer reads out the question and then invites the

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respondent to tell him/her what he/she is thinking. The interviewer then records and notes the process that the respondent uses in arriving at an answer to the question.

The main advantages of this technique are that the interviewer bias is low and the respondent's narration may provide new and unanticipated information. The method is especially valuable when the respondent is articulate. A difficulty of this technique is that many individuals have problems with 'thinking aloud' and tend to simply answer the questions that are asked, without further elaboration.

The main advantage of probing techniques is that the interviewer can focus the discussion on specific areas that appear to be relevant as potential sources of response error. Probing techniques are sometimes criticized for the unusual situation they create, because the interviewer does not simply administer questions and the respondent answers them, but the interviewer interjects by asking 'probing questions'. This disadvantage can be avoided by instructing the respondent in a clear and transparent manner about the procedure of this type of interview prior to asking the questions.

The patient questionnaire was tested by three rare disease patients while the family questionnaire was tested by two parents of children with a complex disease. After translation, NoRo will test both questionnaires with one person each.

4.3.1.2.2 LIMITATIONS OF SELF-ASSESSMENT QUESTIONNAIRES

As is the case with any research relying on individual questionnaire data, this study has to deal with the following limitations:

1. Threat to internal validity

As the same questionnaire will be filled in by the participants at three points in time, this presents a threat to internal validity because as Kirk (2013) argues, a pretest:

- 'can result in familiarity with the testing situation' (Kirk, 2013, p. 26) possibly leading to an unintended effect on the dependent variable
- 'may sensitize participants to a topic, and as a result, of focussing attention on the topic, enhance the effectiveness of the treatment. The opposite effect may also occur. A pretest may diminish participants' sensitivity to a topic and thereby reduce the effectiveness of the treatment' (Kirk, 2013, p. 26).

Considering that there is a nine months-time lapse between each of the tests, it is unlikely that the first problem suggested by Kirk (2013), familiarity with the testing situation, will be a problem because participants are unlikely to be able to base their scores on subsequent tests on previous tests. The second problem presented by Kirk (2013) could be a problem in INNOVCare's pilot study; however this too could be avoided by regulating the information about the experiment provided to the participants²¹ and highlighting to them that the assessments do not serve as evaluation of the individual case managers.

²¹ See section 4.4.2 on the information provided to participants

2. Regression to the mean

In general when observing repeated measurements from the same subjects, extreme scores on the pretest (either very high or very low) are likely to be followed by less extreme scores closer to the true mean, on subsequent measurements; by chance regardless of the treatment (Field & Hole, 2003). The random allocation of participants into the treatment and control groups go a long way to reduce the risk of regression to the mean. In the case that this will still be a problem, relevant measures will be implemented during the analysis of the results; specifically employing the ANCOVA²².

3. Self-report retrospective data

When answering several questions of the ‘soft questionnaire’, interviewees have to rely on recall, which may have implications for the accuracy of the data collected (Colosi & Dunifon, 2006). As questions refer to a relatively short-term period, it is believed that this bias will not significantly affect results.

4. Social desirability

Some questions of the ‘soft questionnaire’ or the mere fact that participants may believe that they are assessing the performance of the case managers, may provoke socially desirable responding. Social desirability describes the tendency of respondents to answer questions in a manner that will be viewed favourably by others (Phillips & Clancy, 1972). To reduce this bias, respondents will be assured of an anonymous administration of their data. Anonymous administration is used so that the person does not feel directly and personally involved in the answers he or she is giving. For the pretest and both posttests, codes instead of names will be used as identifiers. A spreadsheet with the link between names and codes will be stored by the local researchers and will not be handed to the evaluation team. After the experiment is completed, this file will be deleted. Furthermore, it will be clearly explained to the participants that these tests do not act as assessments of the case manager’s work per se.

5. Cognitive dissonance

Cognitive dissonance ‘occurs when participants report improvement even if it did not occur, to meet their own expectation that they should have changed’ (Colosi & Dunifon, 2006, p. 3). It’s hard to rule out this effect. To control for this bias when interpreting results, the ‘soft questionnaire’ will not be relied on solely but in addition results will be reported on a more objective measure – the ‘hard questionnaire’.

4.3.1.2.3 VALIDITY AND RELIABILITY OF THE QUESTIONNAIRE

A ‘reliable’ instrument is one that produces the same measurement if used repeatedly with the same population. Cronbach Alphas on each scale will be run to examine scale reliability. The typical acceptable Cronbach Alpha in social sciences should exceed 0.70.

²² See section 5.2 for more information on the ANCOVA.

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A questionnaire is 'valid' when it measures what it is supposed to measure. There are different ways to assess validity. Convergent validity will be assessed. Generally, convergent validity can be established if two similar constructs correspond with one another. This means that a construct that is similar to the questionnaire instrument will be identified and the relationship between this construct and the instrument will then be assessed. An attempt will then be made to examine whether the items on the 'soft questionnaire' are related to the actual quality of life of patients in order to assess its validity.

4.3.2 QUALITATIVE DATA COLLECTION INSTRUMENTS (FORMATIVE EVALUATION)

Interviews with the case managers will be held every three months to collect data for the social network analysis; however this chance will be used to also qualitatively monitor the progress of the intervention. Should it be deemed necessary to qualitatively survey the patients and their families in the duration of the project, necessary procedures will be set aside.

4.3.3 SOCIAL NETWORK ANALYSIS

According to the project application form, it was deemed necessary to carry out a social network analysis to show the effect of the intervention on the networks of the patients and also the development or change in the communication among different health and social care professionals and organisations involved in the patients' treatment and care. The questionnaire to gather the data necessary for the social network analysis is depicted below. An Excel version of the same is also available. The items highlighted in green will need to only be filled in at the first instance:

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Name of case manager:

Participant code:

Date:

Questions	Response categories
Name of person from other organisation contacted related to the participant's care and management	[Open]
Name of organisation	[Open]
Type of organisation	[Open]
Mode of communication	<ul style="list-style-type: none"> ▪ Telephone ▪ Face-to-face ▪ Email
If telephone, how long was the conversation (ca. in minutes)?	[Time in minutes]
If face-to-face meeting, how long did the meeting last (ca. in minutes)?	[Time in minutes]
What was the purpose of this communication?	[...]
Was this person able to offer the support required for the beneficiary in question?	<ul style="list-style-type: none"> ▪ Yes, this person was able to help me directly ▪ No, but this person was able to point me in the right direction ▪ No, and this person could not point me in the right direction
How would you assess the quality of your communication with this person/organisation today?	<ul style="list-style-type: none"> ▪ Very low ▪ Somewhat low ▪ Somewhat high ▪ Very high
Have you had contact with this person before?	<ul style="list-style-type: none"> ▪ No ▪ Yes
If yes, how long have you known this person for?	[Time in years]
Have you had contact with this organisation before?	<ul style="list-style-type: none"> ▪ No ▪ Yes
If yes, how long have you been in contact with this organisation?	[Time in years]

FIGURE 9: OVERVIEW OF THE SOCIAL NETWORK ANALYSIS QUESTIONNAIRE FOR INNOVCARE

After three months of data collection, ZSI will prepare a matrix of the organisations per participant and the case managers will be required to assess the degree of cooperation. This will be repeated every 3 months during the quarterly interviews with the case managers (therefore 3 times for each participant and their family):

		Degree of cooperation
Organisation A	Organisation B	<input type="checkbox"/> Very weak <input type="checkbox"/> Somewhat weak <input type="checkbox"/> Somewhat strong <input type="checkbox"/> Very strong
Organisation A	Organisation C	<input type="checkbox"/> Very weak <input type="checkbox"/> Somewhat weak <input type="checkbox"/> Somewhat strong <input type="checkbox"/> Very strong
...

TABLE 6: AN EXAMPLE OF MATRIX OF ORGANISATIONS WORKING TOGETHER FOR A PATIENT AND THEIR FAMILY

4.4 PROCEDURE

This section details the procedures for administering the different tools described in the section 4.3 of this report. However, before presenting these procedures, there are three key tasks closely related to these tools which should be conducted by the local implementation team: these are tasks one to three in the following sections. Task four details the procedures for administering the different data collection instruments, their deadlines, target group and whose responsibility it is to administer them.

4.4.1 TASK 1: TRANSLATION OF THE DIFFERENT DATA COLLECTION TOOLS

In preparation for the implementation phase of the experimentation, the team at NoRo needs to translate all the data collection tools from English to Romanian.

To control the quality of the translations, someone else at NoRo, who did not translate the instruments, will be asked to peer review the different instruments after they are translated. In addition, ideally and if possible, these tools should be pretested in the local language following the instructions detailed in section 4.3.1.2.1.

In order to allow the evaluation team at ZSI to work with the collected data after the start of the intervention, the team at NoRo will only need to translate the responses of the open-ended questions into English.

4.4.2 TASK 2: GENERATION OF PARTICIPANT CODES

Participant data will be collected and analysed completely anonymously. However, because each participant will fill in the self-assessment questionnaire at least three times during the pilot study, for the impact analysis, it is necessary to be able to link each questionnaire to a participant at the same time ensuring anonymity. To ensure this, after the random sampling, the team at NoRo should assign a

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code to each of the 120 participants. To ensure that the right participants receive the intervention at the right time, i.e. that the first cohort receive the intervention during the first nine months and the second cohort during the following nine months, the data collection team at NoRo should have a separate file linking the names of the participants and the codes. The case managers should be duly informed of which participants are in the first cohort and which are in the second cohort. Ideally, they should not have access to the file linking the names and the codes to reduce the risk of social desirability from the participants. The participant codes should be created by assigning a number to each of the 120 participants from 001 to 120. During data collection, each participant’s code should be inserted into the data collection instrument. The participants should never have to enter their names.

4.4.3 TASK 3: OBTAINING INFORMED CONSENT

For ethical reasons and to also increase commitment among the participants to take part in the different activities of the pilot study, it is necessary to obtain informed consent from the participants and for children, consent from their parents or guardians. The ‘respect for persons principle’²³ (Commission for the Protection of Human Subjects, 1979), requires participants in a study to be informed about what the study is about, what exactly they will be involved in and to provide a signed consent form agreeing to participate in the study. According to the Belmont report (Ethical Principles and Guidelines for the Protection of Human Subjects of Research), there are three elements that need to be included in the process of seeking consent from participants: ‘information, comprehension and voluntariness’ (Commission for the Protection of Human Subjects, 1979).

To ensure that participants receive sufficient information prior to their commitment to the study, there is a general consensus that the following information should be included: ‘the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.’ (Commission for the Protection of Human Subjects, 1979). However, in some cases where providing the participants with all the information of the study would risk the validity of the experiment, the informed consent can be waived altogether or the participants can be given partial information (Glennerster & Takavarasha, 2013). In such a case according to the Belmont report, no more than minimal risks undisclosed to the participants and an adequate plan to debrief the participants should be put in place (Commission for the Protection of Human Subjects, 1979). In the case of INNOVCare’s pilot study, the participants will be given partial information because it is considered risky to them the exact aims of the experiment, because they may change their behaviour as a result rendering the results of the experiment useless. At the moment there are no greater than minimal risks that are foreseen and a suitable debriefing plan will be made together with the whole INNOVCare consortium.

With regard to comprehension, the information should be presented in a way that the involved persons can easily comprehend it. Special provision should be made for people with limited comprehension for example children or persons suffering from mental disabilities (Commission for the Protection of Human Subjects, 1979). NoRo will build in the consent form in the contracts they are legally obliged to sign with their beneficiaries. Where necessary, the team at NoRo can go through the information available on the

²³ See section 4.5 for more information on this principle

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consent form with individual participants to allow better comprehension. For people with limited comprehension for example children and people with mental disabilities, third parties who are considered to be ‘most likely to understand the incompetent subject's situation and to act in that person's best interest’ (Commission for the Protection of Human Subjects, 1979) will be required to authorise their participation on their behalf. In most cases these will be the family members or guardians of this special group of participants.

Participation in the study is on a voluntary basis. Each participant will be free to participate or withdraw from the study at any time without facing any form of coercion or pressure from all the people involved in the study. NoRo should ensure receipt of all the signed consent forms from those willing to participate before the administration of the pretest.

4.4.4 TASK 4: ADMINISTERING THE DATA COLLECTION INSTRUMENTS

The procedures for administering all the data collection tools are detailed in the report: ‘INNOVCare – WP7: Guidelines for data collection.’

4.4.4.1 Procedure for administering the patient questionnaires

Other than the target group of each of the three versions of the patient questionnaire being different, the procedure for administering these questionnaires is the same. Below is a step-by-step description of the procedure from printing the questionnaires to transmitting the data to ZSI and KI for analysis.

1. **Printing:** NoRo will print out the respective patient questionnaires before the first meeting with the beneficiaries. For the first measurement the PRE versions of the following questionnaires should be prepared:
 - a. Patient-SMILEY:
 - i. At least 18 copies (age group 4-7: n=8 in the 1st cohort and n=10 in the 2nd cohort).
 - ii. A few more copies should be printed, should it be ascertained that some patients 8 years or older have very serious cognitive difficulties to be able to fill in the DCGM-12 questionnaire.
 - b. Patient-8+: About 94 copies should be printed because there are 94 patients out of the 120 who are 8 years and older.
 - c. Patient-SOLO: Number of copies to be printed depends on NoRo’s knowledge of its own patients falling into this category as well as their estimation of the number of external patients falling into this category.

2. **Participant codes:** The survey administrator at NoRo prepares the questionnaires for administration by inserting the participant code on each of the respective questionnaires.

3. **First information:** At the first meeting with the beneficiaries on the 7th of March, before filling in the questionnaires, NoRo should provide the beneficiaries with following information:
 - a. Explanation of the **intervention** or the case management service that will be provided to the beneficiaries - in essence the logic model.
 - b. Explanation of the **evaluation model**:
 - i. **Aim of evaluation:** To determine the effectiveness and suitability of the case management services provided by NoRo to rare and complex disease patients and their families.

ii. **Participants:**

1. As NoRo is providing the service, it is only befitting to offer this service to its own existing beneficiaries in the first instance (n=60).
2. In order to also give non-NoRo beneficiaries the chance to use this service as well, 60 participants were randomly selected from the Salaj county rare disease registry.
3. Due to resource restrictions, the case management service cannot be offered to all 120 beneficiaries and their families for the full duration of 18 months. As a result, they were randomly divided into two groups to either receive the intervention during the first 9 months or the last 9 months.
 - a. This is why many questions refer to '9 months ago'. For the first measurement, this refers to 9 months prior to the start of the intervention. For the second measurement this refers to – now – the start of the service for the 1st cohort. For the last measurement, '9 months ago' refers for the 1st cohort, to the end of the service and to the 2nd cohort, to the beginning of the service.
4. Being in this study is completely voluntary – the participants and their families are not under any obligation to consent and, if they do consent, they can withdraw at any time without affecting any benefits that they are otherwise entitled to or their relationship with NoRo.

iii. **Evaluation procedure:** Completing the questionnaire at three points in time: now, at the beginning of the intervention (March 2017), after 9 months (November 2017) and then after 18 months (July 2018).

iv. **Involved parties:**

1. NoRo: In charge of the intervention delivery
2. ZSI: Responsible for the social impact analysis of the intervention
3. KI: Responsible for the economic impact analysis of the intervention

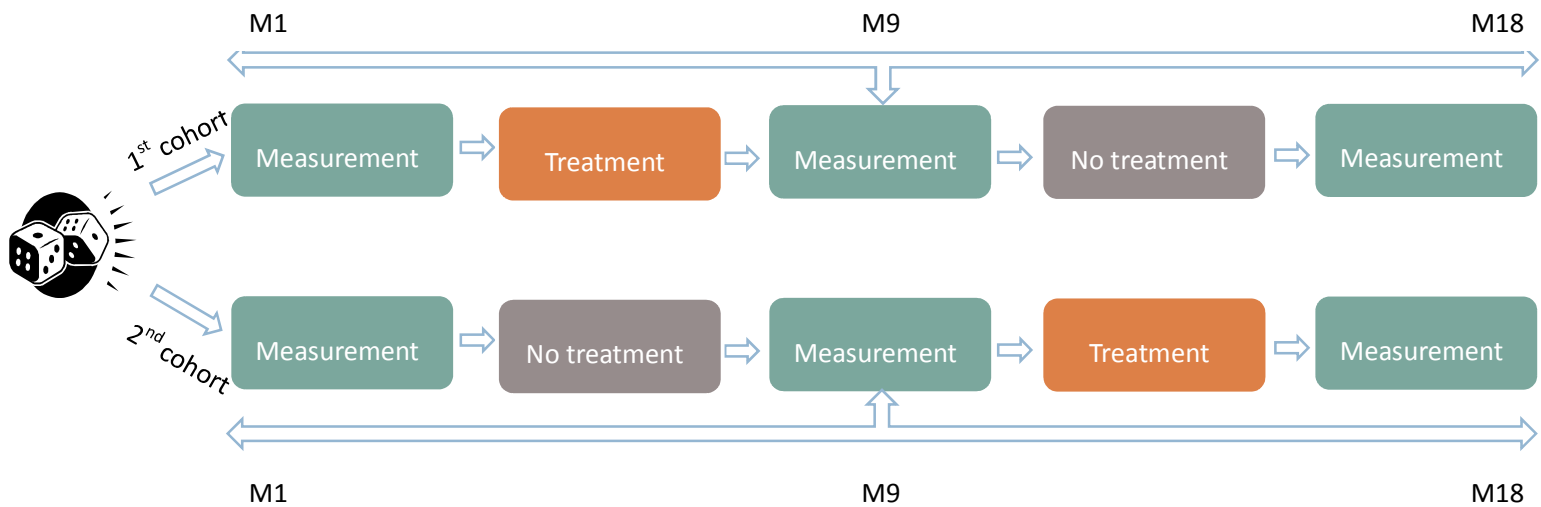
v. **Survey administrator:**

1. To separate the data collection from the implementation of the service, the 'local researcher' (aka. survey administrator) rather than the case managers will administer the surveys.
2. Explain to the participants who the survey administrator is and who the case managers are and how their roles differ from each other.
3. The survey administrator will be present during completion of the survey and can answer any questions related to the survey in general or specific questions of understanding and clarification, but does not directly influence the participants' answers or tell them what to fill in.
4. Where necessary, the survey administrator supports the participants in filling-in the questionnaire either by reading the questions out loud for them or by filling-in the answers into the questionnaire or both.

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5. The survey administrator should as far as possible ensure that the patients fill in the questionnaire fully.
- vi. **Confidentiality and anonymity with data handling**²⁴:
1. All aspects of the study, including results, will be strictly confidential and only limited, designated employees of NoRo will have access to identifiable information about participants - Only the local researcher/survey administrator has access to the key containing the name of the participant and the participant code.
 2. All data submitted to ZSI or KI will be anonymised.
 3. The analysis of the data will not be based on individuals but rather groups and as a result, the findings cannot be traced back to an individual beneficiary.
 4. The beneficiaries are therefore encouraged to be as honest and open as possible with their answers as this may have very large impacts not only in Salaj county or in Romania but in the EU as a whole. This is because the results will determine whether this service should be kept at all and whether it could be transferred to different places.

FIGURE 10: INNOVCARE’S EVALUATION MODEL



- c. Hand-out the **'About the survey'** part of the questionnaires separately to the beneficiaries.

²⁴ See section on data protection below for more detailed information.

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4. **Survey setting:** Regardless of whether the patient survey can be filled in in a group situation or on an individual basis, it is vital, that in as much as possible, the parents, guardians or personal assistants of the patients are not present while the patient is filling in the questionnaire. This is to avoid them influencing the patients' answers.

5. **Survey format:**
 - a. The patient survey should be filled in on paper.
 - b. The survey administrator can support the patient in filling in the survey either by reading the questions out loud for them; by filling in the questionnaire or by doing both. However, while doing this, the survey administrator should try to remain as neutral as possible.

6. **Completion of patient questionnaire:**
 - a. As described above, the assignment of the different versions of the patient questionnaire to the participants highly depends on their ages: 'Patient-SMILEY' suitable for participants aged between 4 and 7, 'Patient-8+' for participants aged 8 and above and 'Patient-SOLO' for adults who are their own main carers.
 - b. However, there are some grey areas: The patient-SMILEY questionnaire can also be filled in by patients who are older than 8 but who have very serious learning or cognitive disabilities. In as far as possible, the patient version of the questionnaires should be filled in according to the defined target groups/age groups. However, it is for the survey administrator to decide whether this is in reality possible or not on a case-by-case basis. In cases where the survey administrator decides that a patient should fill in a different questionnaire to the one he/she would normally be assigned to or when the survey administrator decides to let the participant stop filling in the questionnaire prematurely, a justification should be provided.
 - c. The decision to use the 'patient-SOLO' questionnaire can also only be decided on a case-by-case basis. This is because it is targeted to adult patients who are their own main caregivers. As there is no information to determine which selected participants fall into this category from the already available data, the survey administrator will have to find this information out on a case-by-case basis and therefore provide the person in question with the appropriate questionnaire.
 - d. The survey administrator should encourage the patients to complete the survey fully.
 - e. At the end of the questionnaire, the survey administrator should indicate who filled in the questionnaire: whether the patient autonomously filled in the questionnaire or whether the survey administrator supported them in doing so.

7. **Submission of data:**
 - a. The survey administrator collects the completed questionnaires from the patients.
 - b. She **enters the data on the online survey (Lime Survey) provided**. The data from this survey will be automatically saved and stored on a special ZSI server which is very secure.
 - c. Answers to open questions should be translated into English before being entered into Lime Survey.
 - d. The survey administrator then securely stores the hard copies of the completed questionnaires. This will then be destroyed as soon as it will be confirmed by ZSI that all the data is securely available electronically.

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- e. The deadline of entering the data on the online survey tool will be agreed among NoRo, ZSI and KI.

For the subsequent measurement points, the survey administrator should follow all the 7 steps listed above except for step 3. The survey administrator should take special care in preparing and administering the questionnaires for the second measurement because, the versions of the questionnaires to be administered differ according to the two cohorts. For the second measurement:

1. The 1st cohort gets the POST versions of the patient questionnaires
2. The 2nd cohort still gets the PRE version of the patient questionnaires

For the third measurement, all the participants regardless of which cohort they belong to complete the POST versions of the respective questionnaires.

4.4.4.2 Procedure for administering the family questionnaire

The procedure for administering the family questionnaire is more or less the same as that of administering the patient questionnaires. Below is a step-by-step description of the procedure from printing the questionnaires to transmitting the data to ZSI and KI for analysis:

1. **Printing:** NoRo will print out 120 copies of the PRE version of the family questionnaires before the first meeting with the beneficiaries on the 7th of March 2017.
2. **Participant codes:**
 - a. If possible, NoRo should already put the participant code on each of the respective questionnaires.
 - b. The participant code of the family member completing the questionnaire is the same as that of the patient with an 'f' before so that one can differentiate these. For example the relative of patient 'int001' filling in the family questionnaire, should be given the code of 'fint001' and similarly the relative of patient 'ext001' filling in the family questionnaire, should be given the code 'fext001'.
3. **First information:** Assuming that both the patients and their families will be provided with the first information on the 7th of March together, they should be given identical information as detailed in the section above: '**Procedure for administering the patient questionnaires -> 3. First information**'.
4. **Survey setting:** The survey can be filled in a group setting or on an individual basis. The relative assigned to complete this questionnaire should however answer the questionnaire independently. In case support is required or questions arise, the survey administrator should readily answer these neutrally taking care not to affect or influence the answer of the respondent.
5. **Survey format:**
 - a. The relative of the patient should fill in this survey on paper.
 - b. The survey administrator can support the respondent in filling out the survey either by reading the questions out loud for them; by filling in the questionnaire or by doing both. However, while doing this, the survey administrator should try to remain as neutral as possible.

6. **Completion of family questionnaire:**

- a. In cases where there are no family members to fill in this questionnaire, in the case of the target group of the 'patient-SOLO' questionnaire, then ZSI and KI should be informed as soon as possible, so that they can consider this in the analysis of the data.
- b. The survey administrator should encourage the respondents to complete the survey fully.
- c. At the end of the questionnaire, the survey administrator should indicate who filled in the questionnaire: whether it was a relative of the patient who is also his/her personal assistant or who is not the personal assistant or whether it was someone else.

7. **Submission of data:**

- a. The survey administrator collects the filled in questionnaires from the respondents.
- b. She **enters the data on the online survey (Lime Survey) provided**. The data from this survey will be automatically saved and stored on a special ZSI server which is very secure.
- c. Answers to open questions should be translated into English before being entered into Lime Survey.
- d. The survey administrator then securely stores the hard copies of the completed questionnaires. This will then be destroyed as soon as it is confirmed by ZSI that all the data is securely available electronically.
- e. The deadline of entering the data on the online survey tool will be agreed among NoRo, ZSI and KI.

For the subsequent measurement points, the survey administrator should follow all the 7 steps listed above except for step 3. She should take special care in preparing and administering the questionnaires for the second measurement because, the versions of the questionnaires to be administered differ according to the two cohorts. For the second measurement:

1. The 1st cohort gets the POST versions of the family questionnaires
2. The 2nd cohort still gets the PRE version of the family questionnaires

For the third measurement, all the participants regardless of which cohort they belong to complete the POST version of the respective questionnaires.

4.5 ETHICAL CONSIDERATIONS

In 1979 the U.S. Commission for the Protection of human subjects, in the Belmont report set out three basic ethic principles that should be followed when carrying out scientific research for human participants. Below, these principles are listed, briefly described and INNOVCare's adherence to them is also explained (Commission for the Protection of Human Subjects, 1979):

1. **Respect for persons:** individuals are autonomous agents free to choose their participation or lack of participation in a study. Should their autonomy be diminished for example through disability, they should be protected from harm.
 - INNOVCare adheres to this principle in the sense that participation in the study is voluntary. Each participant willing to participate in the study will be required to provide a signed consent sheet prior the commencement of the activities of the study. Should a participant be unable to provide written consent due to for example their age

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(minors) or disability, this consent will be sought from their family or guardians. Each participant can leave the study at any time. Although only partial information regarding the trial will be provided to the participants to avoid the risk of the validity of the experiment, the most important aspects of the experiment will be provided. Only the exact aim of the experiment, improving the quality of lives of the participants and their families, will be left out.

2. **Beneficence:** an experiment should not knowingly harm the participants and should seek to maximise benefits and minimise harm.
 - The case management approach has been tried and tested in very many different areas. At the moment, there are only a few known implementations of case management within the rare diseases area. However, its success in other fields suggests that it will have a positive impact on the participants. INNOVCare's case management approach will be developed based mainly on consultations with rare disease patients and their families as well as from previous promising practices from similar areas. Hence, it can be categorically said that INNOVCare's intervention will not be harmful to the participants. However, minimal harm could result from withdrawal of treatment especially for the first cohort after receiving the intervention during the first nine months, this is however an aspect of the model that cannot be helped. Including the target group's voice in the development of INNOVCare's case management approach maximises potential benefits and minimises potential harm to the target group.
3. **Justice:** there should be fairness in distribution of the benefits and harms of a study ('hence the need to recruit participants fairly' (Shadish, et al., 2002, p. 281)) and a person should not be denied something that would be of benefit to him or her without good reason or burden should also not be unduly imposed on a person.
 - The experimental design chosen for this study, the 'basic two-condition repeated-measures design / rotation design' ensures that all the participants in the study receive the treatment for the same duration; the only variability is the time that they will receive the treatment. There is no good reason to deny any of the existing rare disease patients at NoRo the treatment, which is anyway expected to have positive effects. As a result, all rare disease patients currently under NoRo's care (n=60) will be included in the study and will also receive the treatment. A further 60 participants will be recruited to the study. This will be done using a random sampling technique which ensures that each person in the target population has an equal chance of being included in the study. All of these new recruits too will receive the treatment.

Due to the fact that all the participants in INNOVCare's study will receive the same treatment for the same duration, the only difference being that some will receive it later than others, overcomes many ethical hurdles often faced with experiments using human subjects. These include for example those involving withholding a potentially effective treatment from participants, say in an independent pretest/posttest control group design where the treatment group receives the treatment and the control group does not or those involving ethical considerations of random assignment. With random assignment, each participant in the eligible sample has an equal chance of being chosen to any of the experimental conditions regardless of for example who needs the treatment most.

Despite this design overcoming such ethical concerns, it still faces three ethical questions:

1. **Duration of the intervention:** From conception of the INNOVCare project, a total duration of 18 months was planned for the intervention. The experimental design adopted for the INNOVCare pilot study provides for a treatment duration of nine months for each participant. The project only has enough resources to employ a maximum of two case managers for the entire duration of the pilot study. It is realistic that each case manager cares for 30 participants at any given time. If one considers an independent pretest/posttest control group design, where only the treatment group receives the treatment, according to calculations based on the programme G*Power, a minimum total sample size of 128 (n=64 per group) would be required for a two-tailed independent t-test given the probability level of $p=0.05$, an anticipated medium effect size (Cohen's $d=0.5$) and a desired statistical power level of 0.8. This would mean that 32 participants are under the care of each case manager for 18 months. Although just above the threshold for each case manager, this would still be considered manageable. However, such a design has the big disadvantage that it withholds treatment from the control group and considering the target group at hand this would not be considered ethical. The most fitting design considering the time and financial resources at hand is the design chosen basic two-condition repeated-measures design / rotation design. However there is a lack of evidence as to whether nine months of treatment would be enough to benefit the participants and at the same time bear impacts large enough to be detected by the model. When the intervention is 'too long', the effects of the intervention may become diluted or crowded out by outside factors not related to the intervention. At the same time, if impact can be generated within nine months, policy makers may not see the point of offering such services to patients for a longer duration. However, if it can be shown with the first cohort that the impact is not long lasting, it might be an argument for policy makers to provide rare disease patients with such a service for a longer duration. Other projects such as Esther, which offer long-term, uninterrupted case management, also cement the argument of offering this service for the long-term.

2. **Discontinuing treatment / withdrawing treatment:** Following on the challenge presented above, for this model to work within the available resources, each participant can only receive a maximum of nine months treatment. This means that treatment for the first cohort, scheduled to receive it during the first nine months of the intervention, will have to be stopped after this period. This could potentially have negative impacts on the participants because 'providing a short-term subsidy to address a long-term problem may be harmful' (Glennerster & Takavarasha, 2013, p. 134). On the other hand, case management as a temporary service is likely to prioritise such support and measures that recipients can continue to benefit from beyond the duration of the intervention.

3. **Withholding treatment from all the whole population:** The planned experimental design for INNOVCare's pilot study requires the recruitment of 60 new patients from the eligible population. In total 120 of the 210 eligible rare disease patients in the county of Salaj will take part in INNOVCare's pilot experiment and also receive the treatment. This leaves 90 eligible rare disease patients out. This could be seen as withholding of treatment that is beneficial because previous studies in other related fields have shown that case management is successful in improving the quality of life of the target group. However due to limited resources in the INNOVCare project, it is deemed currently impossible to include the entire

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population in the study however small. The recruitment of the new patients could also be justified because it will be done using a random sampling procedure which means that each participant has an equal chance of being selected.

The first version of this report was presented to the ZSI and Romanian ethics commissions for evaluation and approval (see appendix for recommendations and approval).

5. RESULTS

Evaluating outcomes means to prove or disprove causal relationship between intervention and outcome measured. The goal of impact evaluation is to reconstruct the counterfactual scenario. To assess the effectiveness of the INNOVCare intervention, descriptive and inferential statistical techniques will be used. Descriptive statistics, which form the basis of every quantitative analysis of data, help to describe the basic features of the data in the study. Inferential statistics will be used to determine if the intervention had a significant effect and eventually how big that effect was.

5.1 DESCRIPTIVE STATISTICS

Descriptive statistics will be applied to describe the basic features of the 'hard' and 'soft' questionnaire datasets. Univariate analysis, such as frequency distribution, measures of central tendency and dispersion techniques will be used to examine main characteristics of the dataset. Using these methods pretest and posttest scores will be inspected and main results will be visualised. This will provide an insight to the general patterns to the data collected.

5.2 INFERENTIAL STATISTICS

In terms of inferential statistics, checking baseline comparability between groups (using independent t-tests) to find out whether randomisation was effective will kick-start the process. Next, further inferential statistical procedures to calculate, whether the INNOVCare Intervention was effective (increase of the participants' quality of life) will be applied.

The dependent variables, which in essence are the indicators for the quality of life of the patients, will be analysed. Further, based on the scales of the 'soft questionnaire' a dependent measure called 'INNOVCare patient quality of life index', which is a composite index of the relevant effective items measuring patient quality of life, will be constructed.

The main independent variables of interest are the 'group' (experimental versus control), the cohorts (first cohort and second cohort) and the measurement time (pretest, posttest and post-posttest). To control for extraneous variance, the 'blocking variables' can be added as an additional independent variable in the design as some part of the variance can be explained by these variables. However, this has to be thoroughly considered because as Verma (2016, p.16) argues, 'by the inclusion of the extraneous variable in the design, the error variance is reduced but at the same time degrees of freedom of error variance also gets reduced. Thus the design will only become more efficient when the extraneous variable is known to affect the criterion variable significantly.'

If the preconditions for parametric statistics are fulfilled, dependent t-tests will be used to analyse differences between post-results of experimental and control group and analysis of variance (ANOVA)

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for repeated measures to test differences between and within groups (Field, 2013, Field & Hole, 2003, Girden, 1992, Verma, 2016).

The repeated measures ANOVA has one between subjects factor (treatment group) and one within-subjects factor (time, within cohort – treatment & control measurements). “Repeated measures” is a term used when the same entities participate in all conditions of an experiment or provide data at multiple times in time (Field, 2013, p. 544) – both of these situations are true for the INNOVCare pilot study. On one hand, because each participant will take part in all the experimental conditions and on the other hand, because data will be collected from each participant using the same data collection instrument at three different points in time. The research questions which will be analysed with this approach are:

1. Does the mean change in the outcome from pretest to posttest differ between the first cohort and the second cohort during the first nine months?
2. Does the mean change in the outcome from pretest to posttest within the first and second cohorts during the duration of the pilot study (where each group is acting as its own control)?

This is directly measured by the time*group interaction term in the repeated measures ANOVA. This will measure the ‘systematic variance’ which is the measure of variation resulting from manipulating the independent variable’ (Verma, 2016, p. 5)

In case significant pretest differences between experimental and control group will be detected, it will be controlled using an Analysis of Covariance (ANCOVA) procedure. In ANCOVA, the dependent variable is the posttest measure. The pretest measure is not an outcome, but a covariate. This model assesses the differences in the posttest means after accounting for pretest values.

The ANCOVA approach answers the following research question: ‘Do posttest means, adjusted for pretest scores, differ between the groups (between and within the two cohorts)?’

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6. ANNEX 1 Patient Questionnaire – confidential

7. ANNEX 2 Family Questionnaire – confidential

8. ANNEX 3 Certificate of NoRo Ethical Committee

ETHICAL CLEARANCE CERTIFICATE

Registration number: **160/21032017**

Project title: **INNOVCare - Innovative Patient-Centred Approach for Social Care Provision to Complex Conditions – WP6 and WP7**

About the project: The research evaluates the effects of a case management approach on the quality of life of rare disease patients in Salaj, Romania: a randomised control trial of efficacy

Main Researcher: Hotlgrewe Ursula (Zentrum für Soziale Innovation: ZSI)

Other researchers: August Gächter, Juliet Tschank, Katharina Handler, Dr. Stefanie Konzett-Smoliner

On behalf of the ethical committee of the Romanian Prader Willi Association, prof. dr. Emilia Severin, hereby confirms the awarding of the ethics certificate based on the undertakings contained in the mentioned project and on research methods and instruments submitted for fulfilling the study. The Researchers may therefore commence with the research, using the reference number indicated above.

Romanian Prader Willi Association and the ethical committee must be informed immediately of:

- Any changes in the conditions for which this certificate was awarded;
- Any events that impact upon the ethical conduct of the research.

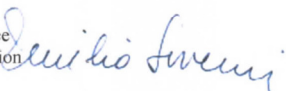
The Main Researcher must report, in writing, as the project timetable and the financing body requires.

The Romanian Prader Willi Association retains the right to:

- Withdraw or amend this Ethical Clearance Certificate if:
 1. Any unethical principal or practices are revealed or suspected;
 2. Relevant information has been withheld or misrepresented.
 3. Regulatory changes of whatsoever nature so require;
 4. The conditions contained in the Certificate have not been adhered to.
- Request access to any information or data at any time during the course or after completion of the project.

Best regards,

prof. dr. Emilia Severin
 president of the ethical committee
 Romanian Prader Willi Association



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9. Annex 4 Recommendations of ZSI Ethical Commission



ZENTRUM FÜR SOZIALE INNOVATION
CENTRE FOR SOCIAL INNOVATION

ZSI Ethics Commission

Recommendations for the Project

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The Ethics commission provides its recommendations on the basis of the project description of work, the Methodological Report, the documentation for the Ethics Committee of the Romanian partner and a discussion with the project team.

Respondents are clearly vulnerable in multiple ways and data are sensitive: children with disabilities and their families. Rare diseases in a regional context make it difficult to ensure anonymity of respondents. Since ZSI is not collecting data itself, the partnership will need to sign confidentiality agreements.

Informed consent: the Methodological Report says not all aims of the study will be explained in the consent form. INNOVCare researchers explain that this applies to the aim of evaluating case management. In order not to bias responses by personal relations with the case manager this purpose will be explained in somewhat general terms.

Data are being collected and analysed for two distinct purposes:

1. Recruiting “new clients” from the 215 RD patients in the region, based on the county’s database and stratification along age and gender.
2. Surveys to be administered to participants (or their guardians in cases of children and people unable to reply by themselves) and to their families at three points in time to measure the impact, asking for information about rights, entitlements, service quality and quality of life as well as social-structural data on household income, education level etc. This is co-developed with Karolinska Institutet in charge of socio-economic impact evaluation.

For anonymity, code numbers can be used. Names and addresses are needed only for identifying project participants from the RD patients and need not be transferred to ZSI.

With the sensitivity and specificity of the questionnaire data, anonymity by codes is not sufficient. Access to data will be handled restrictively: Only researchers involved with data analysis receive access to the raw data, data will be shared with other project partners and made available in the project’s publications only in aggregated form to ensure participants cannot be identified. A procedure for secure data storage on a distinct password-protected drive, encrypted transfer and also data deletion will be developed by the project team in collaboration with ZSI’s IT department.



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