Institution: Newcastle University

Unit of Assessment: 21 Sociology

Title of case study: Improving the Governance and Efficacy of Rare Disease Research by Ensuring the Integration of Patients' Perspectives

Period when the underpinning research was undertaken: 2006-2017

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Simon Woods	SW Professor	SW 2003-2020,
Pauline McCormack	PM Senior Lecturer	PM 2008-2020

Period when the claimed impact occurred: 2014-2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Woods and McCormack have significantly improved the governance of international research into rare diseases (RD), which affect 400,000,000 people globally, to the benefit of patients and their families. They achieved this through bringing patients, clinicians and researchers together in novel governance bodies and improving the capacity of all involved to recognise the nuance and validity of each other's perspectives. Patients' voices would traditionally have been excluded from research governance before Woods' and McCormack's pioneering research. Changing this was especially important as their work engaged with some of the first patients to be involved in 'big data' research. Using a suite of qualitative methods and co-production, they rendered significant benefits to the global population of RD patients by: (1) enabling and supporting patient representation in research governance, (2) developing patient-informed governance procedures, and (3) improving international standards of care.

2. Underpinning research

Woods and McCormack are based in the Policy, Ethics and Life Sciences Research Centre (PEALS) at Newcastle Sociology. PEALS is internationally recognised for its empirically informed socio-ethical research on innovations in medical sciences. Their work has focused on patients with rare diseases (RD) that are often genetic in origin, which while individually rare, collectively affect 400,000,000 people globally. RD medical research is complex and intrusive, raising significant social and ethical challenges for patients and their families. The patient organisation Rare Disease Europe (EURORDIS) in 2008 called for strategic co-ordination of research policies and infrastructure in which patients should be accorded a greater role. Woods and McCormack have addressed these challenges through their contribution to major international research projects funded by the European Commission (EC). This case study focusses on two projects: TREAT-NMD and RD-Connect.

A key ambition for both projects was to unite the global diaspora of RD researchers in order to maximise the potential for better care and treatment for RD. Woods and McCormack were invited to lead research within the projects based on their knowledge of the socio-ethical complexities of large-scale medical research and their expertise in enabling patient involvement.

TREAT-NMD (2007-present) was initially funded as an EU Network of Excellence (2007-2012), but continues now as the TREAT-NMD Alliance. The Alliance continues to improve international research and clinical practice related to rare neuromuscular diseases. In the initial EU project Woods (Co-investigator and work-package leader) with McCormack (Research Associate) drew on theories of patient autonomy, activism and bio-sociality to inform their research on patient representation. Their research identified that governance challenges in RD research included substantive issues around patient involvement, the sharing of sensitive data, and the participation of children in clinical research. Working collaboratively with Patient Organisations

(POs) they established in 2008 a novel governance body: The Project Ethics Council (PEC) **[PUB 1]**. The PEC enabled clinicians and scientists to work alongside patient representatives in a collegiate and non-hierarchical structure, which both informed the management of project-related ethical issues and provided a site for Woods' and McCormack's ongoing research on the inclusion of patient representatives in research governance. This work became a virtuous circle for improving patient involvement and led clinical researchers to take seriously the knowledge and priorities of patients. Woods and McCormack were thus in the vanguard of participatory approaches to research governance. Four of the six research publications cited here were co-produced with POs.

Historically, normative standards for the governance of medical research focused on non-exploitation of patients. Woods' and McCormack's research with the PEC and with POs critically examined this consensus and identified a particular 'activist' element of the patient perspective that sought to influence the research agenda **[PUB 2]**. They also critiqued the 'therapeutic misconception', a concept in clinical trials which exists when a research participant falsely believes that the aim of the research is to provide beneficial treatment when the actual purpose is to determine whether there are any benefits at all. Woods and McCormack found that parents' motivations when consenting for children to participate in a clinical trial were highly nuanced, and that they needed specific support including carefully presented information about the research. The role of POs in facilitating research was also explored and a potential for over-promoting participation to parents was found **[PUB 3]**.

RD-Connect (2012-present) created a platform that continues to shape international research practice in the field of rare diseases by enabling the use of 'big data' through connecting databases, patient registries, biobanks and clinical bioinformatics internationally. Woods (Co-investigator) and McCormack (Senior Research Associate) led work that examined the challenges of large-scale sharing of sensitive clinical data and bio-samples across international boundaries (EC-funded 2012-2018). They further developed and applied the novel methodology from TREAT-NMD that allowed *research* on patient participation and *actual participation* to happen in concert, and for each to inform and reinforce the other in real time. This interwove (i) strategies for patient inclusion in research design and governance, (ii) deliberative conversations between RD patients, clinicians and scientists about how research infrastructures should be instituted and operated, and (iii) research, co-produced with RD patients, about their lived experiences relevant to participation in RD research. This latter work involved some of the first patients to be involved in 'big data' research, making their research internationally significant **[PUB 4]**. Patients were found to be supportive of sharing their bio-samples and personal data with multiple researchers if they were treated with respect and reciprocity. Further research focussed on issues around informed consent for data and bio-sample sharing across multiple research projects and international boundaries **[PUB 5]**. This led to an International Charter of Principles for data sharing for genomics research which demonstrates that RD research can be both patient-centred and sustainable **[PUB 6]**.

Woods' and McCormack's findings from their research in these projects revealed that patients had strong convictions on some of the central ethical issues in RD research, sometimes distinct from professionals, which they were able to articulate and defend **[PUB 1,2, 4 and 5]**. Patients could also contribute to research leading directly to improvements in care **[PUB 6]**. However, both patients and their representatives needed support in developing their capacity to contribute to research governance **[PUB 3]**.

3. References to the research

Publications listed below collectively represent research of at least 2* quality based on REF criterion of significance, rigor and originality, with all issuing from 'gold star' funded research projects (European Commission grants) and being rigorously reviewed in high quality journals and through internal and external REF review processes.

*[PUB 1] McCormack, P., Woods, S., Aartsma-Rus, A., Hagger. L., Herczegfalvi, A., Heslop, E., Irwin, J., Kirschner, J., Moeschen, P., Muntoni, F., Ouillade, M.C., Rahbek, J., Rehmann-Sutter, C., Rouault, F., Sejersen, T., Vroom, E., Straub, V., Bushby, K., Ferlini, A. (2013) 'Guidance in

social and ethical issues related to clinical, diagnostic care and novel therapies for hereditary neuromuscular rare diseases: "translating" the translational'. *PLOS Currents Muscular Dystrophy*. Jan 10. Edition 1. https://doi.org/10.1371/currents.md.f90b49429fa814bd26c5b22b13d773ec

[PUB 2] Woods, S. and McCormack, P. (2013) Disputing the ethics of research: the challenge from bioethics and patient activism to the interpretation of the Declaration of Helsinki in clinical trials. *Bioethics*. 27(5): 243-250. https://doi.org/10.1111/j.1467-8519.2011.01945.x

[PUB 3] Woods, S., Hagger, L.E., and McCormack, P. (2014) Therapeutic misconception: hope, trust and misconception in paediatric research. *Health Care Analysis*. 22(1), 3-21. https://doi.org/10.1007/s10728-012-0201-8

*__[PUB 4]__ McCormack, P., Kole, A., Gainotti, S., Mascalzoni, D., Molster, C., Lochmüller, H., Woods, S. (2016) '"You should at least ask". The views of rare disease patients and advocates on large scale systems for data and biosample sharing.' *European Journal of Human Genetics*. 24: 1403-1408. 24: 1403-1408. https://doi.org/10.1038/ejhg.2016.30

*__[PUB 5]__ Gainotti, S., Turner, C., Woods, S., Kole, A., McCormack, P., Lochmüller, H., Riess, O., Straub, V., Posada, M., Taruscio, D., Mascalzoni, D. (2016) 'Improving the informed consent process in international collaborative rare disease research: Effective consent for effective research.' *European Journal of Human Genetics*. 24:1248-1254. https://doi.org/10.1038/ejhg.2016.2

*__[PUB 6]__ Mascalzoni, D., Dove, E., Rubinstein, Y., Dawkins, H., Kole, A., McCormack, P., Woods, S., Riess, O., Schaefer, F., Lochmüller, H., Knoppers, B., Hansson, M.. (2015) 'International charter of principles for sharing bio-specimens and data.' *European Journal of Human Genetics*. 23(6): 721-728. https://doi.org/10.1038/ejhg.2015.237

***Co-produced with patient organisations**

GRANTS:

1. Volker Straub (PI), Kate Bushby (PI) and Simon Woods (Co-I) 'TREAT-NMD', Funded by European Commission of the European Union ID 36825, 2007-2012, (GBP1,357,222)

2. Hans Lochmüller (PI) Kate Bushby (PI) and Simon Woods (Co-I) 'RD Connect', Funded by European Commission of the European Union ID 305444, 2012-2018, (GBP1,071,782)

4. Details of the impact

Woods' and McCormack's research has changed and improved the practices of RD research governance globally, by ensuring the inclusion of patient representatives and their opinions. This has resulted from the careful development of an integrated community of patients, researchers and clinicians who now share a deep and nuanced understanding of each other's perspectives on how RD research should progress.

1. Patient representation in research governance

The impact of Woods' and McCormack's research in TREAT-NMD is evidenced in the inclusion of patient representatives in the governance structures of the continuing (post-2012) TREAT-NMD Alliance (hereafter The Alliance). The Alliance is made up of 258 organisations representing thousands of scientists, clinicians, and patient advocates from across the globe. The Alliance is supported by the TREAT-NMD Project Ethics Council (PEC) established by Woods and McCormack in which 40% of members are patient advocates. The PEC is both responsive and proactive regarding ethical issues related to RD research. As the Chair of the Alliance comments: *'It is currently more and more common practise to involve patient representatives in all aspects of therapy development. However, when Professor Woods and Dr McCormack initiated the PEC, this was not yet the case. Still, they always put the patients first,*

not only within PEC, but also within TREAT-NMD and the projects that it spawned, ensuring the patient voice was heard during meetings' **[IMP 1]**.

RD-Connect was established to further improve RD research through international collaboration and data-sharing. A PEC modelled on TREAT-NMD was established in 2012, chaired by McCormack, with Woods as a member. The methodology used in TREAT-NMD was further developed and a Patient Advisory Council (PAC) established (2013) in addition to the PEC, to support patient representatives, to develop capacity and to discuss issues in a safe space. As the project manager of RD-Connect comments: '*The legacy of this work is that these two bodies continue (as of Sept 2020) to advise 79 of the world's leading RD laboratories and clinics and positively influence the working practices of their scientists and clinicians'* **[IMP 2]**. The transferability of this approach was demonstrated when the model of the patient inclusive PEC and PAC was adopted by two other EC-funded research initiatives, EURenOmics (rare renal diseases) and NeurOmics (rare neurological diseases). The three projects formed a joint Rare Disease Patient and Ethics Council (RD-PEC 2013, chaired by McCormack 2013-2018), with a remit to cover 129 health, research, government, and industry organisations in 60 countries worldwide – advising clinicians and scientists and producing ethical opinions on a range of issues. An example of this work is **[IMP 3]**, where RD-PEC coordinated a response with other relevant organisations to a 2014 Council of Europe (CoE) consultation on 'research on biological materials of human origin'. The response, which would traditionally have come only from elite groups such as clinicians and bioethicists is all the more powerful for being jointly authored by patients, scientists and clinicians. It emphasised the importance of balancing individual citizen's rights to privacy and to benefit from medical research. A key statement in the response noted the importance to patients of their data being shared across different international research projects, a practice previously seen as ethically problematic by clinicians.

2. Patient informed governance procedures

Woods' and McCormack's findings on patients' concerns about privacy, security and their ethical protection in research formed the basis of further guidelines and impacted on practises of RD-Connect researchers. Patient concerns significantly informed the publication of an International Charter of Principles for data and bio-sample sharing (The Principles 2015) and a guide to informed consent processes for international data sharing (Consent Guide 2015). These were developed following 12 interdisciplinary workshops jointly organised by Woods and McCormack between 2013 and 2018, involving over 300 patients, scientists and clinicians. The workshops equipped participants with the capacity to develop and implement their ideas in the light of a mutual, deep and nuanced understanding of all parties involved in RD research.

The Principles and Consent Guide were subsequently adopted via a peer-review process (in August 2015 and Sept 2016), by the International Rare Diseases Research Consortium (IRDiRC) as Recognized Resources for researchers. The Chair of IRDiRC comments: '*the label* (Recognized Resource) *was created to highlight key resources, that if used more broadly would accelerate the application of rare disease research into clinical care and treatment. The label is an assurance of quality and appropriateness'* **[IMP 4]**. The IRDiRC has 35 member organisations worldwide, consisting of patient organisations, research funders and biotech companies who have jointly committed to spending over GBP350,000,000 on RD research. The beneficiaries of the adoption of The Principles and Consent Guide include the patients whose data and bio-samples are shared, and the scientists and clinicians working to improve diagnosis, treatment and care who can utilise these data within a patient-centred framework.
The International Charter of Principles was translated in 2015 into a Code of Conduct (revised 2018) **[IMP 5]** which is a practical agreement providing methods and template documents to be used by researchers to enable ethical research. Written compliance with the Code of Conduct is now a condition of access to the RD-Connect Platform and over 400 researchers have signed up, thereby committing to implementing its patient-centred values in their work.

3. Improving standards of care

Woods' research on enabling patient representation in TREAT-NMD led directly to an invitation in 2016 to join international experts in revising the international standards of care (SoC) for the

rare genetic disease spinal muscular atrophy (SMA). Woods led the working group on ethics and palliative care, drawing on Delphi methods to canvas patient opinion to ensure that patient views on ethical issues and concerns about palliative care were addressed in the SoC **[IMP 6]**. Published in 2017, the SoC is now *the* reference point for clinicians dealing with SMA patients, evidenced by more than 400 citations in clinical journals. Additionally, they have been widely adopted by POs. Woods also contributed to a patient-friendly version in 2017 **[IMP 7]**. This version has been translated from English into four other languages and has been distributed by all the major international SMA patient organisations. As one PO states, the SoC serve '*as resources for clinicians, in order to ultimately improve quality of care for individuals with SMA*' (CureSMA) **[IMP 7]**, and another PO described it as '*a major upgrade over what was available before*' (TreatSMA) **[IMP 7]**.

Woods' and McCormack's evidence-based advocacy of patient involvement in RD research has also been used to ensure that RD contexts are considered in the development of policies and practises concerned with medical research involving children. For example, they were invited to provide evidence to the Nuffield Council on Bioethics (NCoB) working group (2013-15) on the ethics of children's participation in research. As the Director of NCoB says: *'The report has been recognised as an important contribution to the field of paediatric research both in the UK and internationally… The ethical framework and practical recommendations made in the report are enabling regulators, funders and researchers to carry out good research with confidence'* **[IMP 8]**. The NCoB report and practice framework contain several references to Woods' and McCormack's research findings, and it has gone on to be widely cited and adopted. In the UK the Royal College of Paediatrics and Child Health has adopted the report as one of only five recommended sources of ethical guidelines for clinical researchers working with children, and the European Medicines Agency and a European network for paediatric research have highlighted the importance of the NCoB report **[IMP 9]**. This means that many thousands of children and their families experience improved ethical practice when participating in medical research.

Woods and McCormack have, in summary, made significant and lasting contributions to improving the international standards of ethical care of patients (particularly children) and their families who are involved in research into the diagnosis and treatment of rare genetic diseases. This was achieved by demonstrating the benefits of altering the governance of these activities to include patient voices and contributing significantly to the building of a research infrastructure in which patients and professionals share a deep understanding of each other's perspectives and priorities.

5. Sources to corroborate the impact

[IMP 1] Testimonial: Current Chair of TREAT-NMD Alliance.
[IMP 2] Testimonial: Former Project Manager of RD-Connect.
[IMP 3] Joint response to the Council of Europe's public consultation concerning 'research on biological materials of human origin' - the response includes patient representatives, clinicians and scientists from five international rare disease research collaborations.
[IMP 4] Testimonial from the Chair of IRDiRC outlining the adoption and importance of the Charter of Principles and Consent Guide for international research collaborations.
[IMP 5] RD-Connect 5.a: PAC and PEC web pages, 5.b: Researcher link to the Code of Conduct, 5.c: Email from RD Connect Platform Manager confirmation of the 400+ signatories, 5.d: Code of Conduct, 5.e: IRDiRC Recognised resources web page.
[IMP 6] Published report on the consensus workshop that collated the findings from the Delphi method used by Woods and others to engage patient opinion leading to revised SoC.
[IMP 7] 7.a, 7.b: The Standards of Care published version, 7.c: SoC Patient version, 7.d: CureSMA, 7.e: TreatSMA - website pages endorsing the Standards of Care.
[IMP 8] Testimonial from the Director of the Nuffield Council on Bioethics including evidence of the international impact of the report's recommendations and ethics framework.
[IMP 9] Links to the Nuffield Council report by: 9.a: Royal College of Paediatrics and Child Health, 9.b: European Medicines Agency, 9.c The European Network of Excellence for Paediatric Research.