Institution: University of York		
Unit of Assessment: 2 - Public Health, Health Services and Primary Care		
Title of case study: Improving management of neutropenic sepsis in paediatric cancer patients		
Period when the underpinning research was undertaken: 2012 - 2020		
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:**
Bob Phillips	Senior Clinical Academic Consultant Paediatric Oncologist	2008 - present
Jess Morgan		2016 - present
Lesley Stewart	Clinical Lecturer	2006 - present
Rosalind Wade	Professor Research Fellow	2001 - present
Period when the claimed impact occurred: August 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

York research has underpinned the introduction of risk-stratified management of neutropenic sepsis in children and young people (CYP) with cancer. Our research on tests and risk-based intervention directly informed National Institute for Health and Care Excellence (NICE) clinical guidelines. Our subsequent research augmented this and underpinned change in UK management of NS in paediatric oncology. National audits demonstrated increasing uptake, which accelerated in 2020 when risk stratified management became central to the COVID-19 response. Risk stratification has shortened in-patient stays, reduced management costs, improved antimicrobial stewardship, reduced unnecessary testing, improved wellbeing; and is estimated to save the NHS over 5000 bed days and GBP 6 million annually. Our research also informed international guidelines, with evidenced changed care in Australia and North America.

2. Underpinning research (indicative maximum 500 words)

Neutropenic Sepsis (NS - also known as febrile neutropenia) affects 80% of children and young people (CYP) undergoing anti-cancer treatment and accounts for over 3,000 UK hospital admissions annually (anti-cancer therapy is immunosuppressive, increasing risk of life-threatening infection). Patients require careful management if they develop fever. However, fever is often caused by simple viral infection and most CYP are at low risk of developing significant complications. Prior to our research, CYP presenting with NS had every episode managed by hospital admission for ≥ 7 days and treated with two antibiotics. Most had a chest x-ray on admission and continued antibiotic treatment even if no infection was detected. Whilst this approach treated any infection present, it also led to unnecessary hospitalisation and avoidable distress for low risk CYP and their families. It also increased the risk of antimicrobial resistance. Since 2008, Bob Phillips, Jess Morgan, Rosalind Wade and Lesley Stewart have, with international colleagues, evaluated the treatment and management of NS through a series of connected systematic reviews (SR), individual participant data (IPD) syntheses, qualitative research studies and clinical trials.

(1) Risk stratification

Risk stratification enables use of shorter duration and less intensive (oral) antibiotics in NS patients at lower risk of severe bacterial infection. Our SR **[A]** identified the most promising prediction rules and that predictive ability appeared linked to the geographical area in which studied. We then established the 'Predicting Infectious Complications in Children with Cancer' (PICNICC) international collaboration to explore whether a more robust and globally applicable rule could be created. PICNICC included 22 research groups in 19 countries and collected IPD for 5,127 NS episodes in 3,504 patients. We developed an initial global risk prediction model and demonstrated that teenagers could not be assessed in the same way as children or adults. **[B]** In Australia, a new primary PICNICC study was set up to generate data to test the PICNICC model and, when unable to validate the global model, to adapt and implement a rule for an Australian population. The resulting 'Australia-UK-Swiss' prediction score was in turn validated

for the UK population, using the PICNICC dataset, as part of York's rapid response to SARS-CoV2, enabling improved stratification of patients and further shortening periods of hospitalisation **[C]**.

(2) Reducing durations and intensity of antibiotic therapy
Our SR exploring acceptability and implementation of reduced intensity therapy for children at lower risk of severe infection was inconclusive, so we undertook primary research to identify barriers to implementation, and proposed approaches to counter them **[D]**. With PICNICC colleagues in Sheffield we completed a detailed review of UK primary data on the duration of antibiotic use, which confirmed that a shorter duration of empiric therapy was safe and effective for NS patients. Both informed the implementation of risk stratification as part of the COVID-19 response.

(3) Utility of chest x-ray on admission
SR and meta-analysis generated convincing evidence that there was no benefit in undertaking chest x-rays (to detect 'hidden' chest infections) when patients presented at hospital. This was a definitive finding requiring no further research **[E]**.

(4) Utility of biomarker blood tests to predict/identify severe infection:
SRs of serum biomarker tests to identify those at risk of severe infection revealed considerable uncertainty in utility and value **[F]**; our feasibility trial of procalcitonin as a biomarker/predictor is currently underway.

As noted in section 4, York underpinning research **[A][E][F]** has been incorporated in national and international clinical guidelines for which Phillips was the clinical (co-) lead. These guidelines, augmented by additional York research **[B][C][D][F]** drove changes in clinical practice. It also underpinned national management strategy during the SARS-CoV2 pandemic**.**

3. References to the research (indicative maximum of six references)

A. (2010) **Phillips, R. Wade, R. Stewart, L.** & Sutton, A. Systematic review and meta-analysis of the discriminatory performance of risk prediction rules in febrile neutropenic episodes in children and young people. European Journal of Cancer 46(16):2950-2964. 10.1016%2Fj.ejca.2010.05.024 ***^#** (update published 2012***§**).

B. (2016) **Phillips R.S.**, Bhuller K., Sung L., Amman R.A., Tissing W.J., Lehrnbecher T. & **Stewart L.A**. Risk stratification in febrile neutropenic episodes in adolescent/young adult patients with cancer. European Journal of Cancer 64:101-106. 10.1016/j.ejca.2016.05.027 ***§**

C. (2021) **Phillips, B**. & **Morgan, J.E**. Meta-analytic validation of new 'AUS' febrile neutropenia risk score. Pediatric Blood and Cancer 68(1)(First published: 25 July 2020)10.1002/pbc.28580*

D. (2018) **Morgan J.E.**, Hassan H., **Stewart L.A., Phillips R.A.** & Atkin K. "The quest for certainty regarding early discharge in paediatric low risk febrile neutropenia: a multi-centre qualitative focus group discussion study involving patients, parents and healthcare professionals in the UK. BMJ Open 8(5) 10.1136/bmjopen-2017-020324 ***&**

E. (2012) **Phillips R., Wade R.,** Westwood M, Riley R, Sutton A. Systematic review and meta-analysis of the value of clinical features to exclude radiographic pneumonia in febrile neutropenic episodes in children and young people. Journal of Paediatrics and Child Health 48(8): 641-8. 10.1111/j.1440-1754.2011.02211.x ***§**

F. (2012) **Phillips, R., Wade, R.** Lehrnbecher T, **Stewart, LA**. Sutton, A. The value of initial biomarkers in predicting adverse outcome in febrile neutropenic episodes in children and young people with cancer: a systematic review and meta-analysis. BMC Medicine; 10:6: 10.1186/1741-7015-10-6 ***^** (2 updates published 2013, 2019 ***§**).

[A] and **[F]** have subsequent update publications (as noted).

*****peer reviewed publication; undertaken as competitive peer reviewed fellowships funded by MRC**^** NIHR**§**; and as an open Fellowship reviewed by the Candlelighters charity Trustees **&; #** REF2021 output.

4. Details of the impact (indicative maximum 750 words)

(1) Impact on UK clinical practice

York research directly informed the NICE Guideline on the Prevention and Management of NS (for all ages of patients) [NICE CG151]. This included preliminary and unpublished findings that were shared by Phillips as part of his membership of the guideline development group; specifically providing evidence for adoption of a risk stratified (low-risk) approach [1.5.1 and 1.5.2] **[A]**, use of a single inflammatory biomarker [1.4.1.2] **[F]**, and discontinuing the use of routine chest X-rays on admission [1.4.2.2] **[E]**. The guideline was first published in 2012, but remains current; in 2020 NICE decided that recommendations required no substantial changes **[1]**. Subsequent York research including **[B]** and updates to **[A]** and **[E]** provided further and specific evidence on managing NS in CYP. Thus, York's underpinning research has supported clinical decision making since 2012 and throughout the current REF period.

"*Research from the University of York on neutropenic sepsis (NS) in children and young people (CYP) with cancer directly informed NICE CG151, the NICE Guidelines on the Prevention and Management of NS, in particular providing supporting evidence for adoption of a risk stratified approach, which subsequently results in both benefits for patients and resulting cost savings for the NHS in terms of earlier discharge lower intensity antibiotic therapies and discontinuing use of routine chest x-rays on admission.*" CEO, Children's Cancer and Leukaemia Group (CCLG) **[2]**

Repeated 14-day snapshot audits of UK NS admissions by the national network of heath care professionals treating CYP with cancer (the CCLG) demonstrated increasing alignment with NICE guideline recommendations and with our research findings, which were specific to paediatric patients. Published audits showed that:

- Implementation of risk stratification programmes increased from 36% in 2012 to 75% in 2017, reducing (in-patient) stays from a median of 5 to 3.5 days.
- Broad spectrum intravenous antimicrobial use decreased; the proportion of patients who either transitioned from intravenous to oral antibiotics or stopping at 48 hours after admission increased from 43% to 76% in the same period.
- Centres no longer undertake routine chest X-rays.
- Despite increasing use of serum inflammatory biomarkers in other paediatric specialities, use in this patient group has been minimal. **[2]**

The CCLG CEO noted how this impacts on patients and families:

"The impact of this important work is multifactorial, from informing guidance to supporting its implementation and changing practice across the UK, to cost savings for the NHS, and informing international clinical practice. Ultimately of course, I would argue the benefits to young patients and families are the most important impact of this work. A childhood cancer diagnosis is a distressing, isolating and challenging time for any family, and any work that improves provision of supportive care will improve quality of life. We know from our work with patients and families that seemingly small things make a huge difference – a shorter hospital stay, not undertaking additional tests and procedures, or being able to go home with oral medication rather than a sustained admission for IV therapy – impacting in a number of domains on quality of life including mental wellbeing and stress, finances, and family life." **[2]**

Implementation accelerated in 2020 with the emerging SARS-CoV2/COVID-19 pandemic. UK paediatric oncology services were prioritised to continue delivering therapy but urgently required a strategy to safely minimise hospitalisation and switch to lower-toxicity approaches, including full implementation of risk-stratified management of NS, and to shorten treatment duration even

further. Within two weeks, the York team validated the PICNICC Australia 'AUS' risk prediction score for a UK population **[C]** and evaluated use of very short duration admission, leading to a new agreed national strategy through the CCLG. Acknowledging provider fears about risks of home-based care **[D]** with clear messaging and consistent information, and supporting the use of a 'virtual ward' with daily structured phone calls to parents was also part of the response.

Health care provider implementation tools and patient-information materials based on York research were developed, as was an evaluation package to assess breadth and quality of uptake. The importance of York input to the pandemic response was confirmed by both the Chair **[3]** and CEO **[2]** of the CCLG:

> *"…the York team validated the PICNICC Australia 'AUS' risk prediction score for a UK population and evaluated its use within two weeks. In turn this led a new agreed national strategy through the CCLG. This extremely short turn around period would not have been possible without the underpinning programme of research carried out by the York team who had validated the approach to risk stratification and empiric treatment of febrile neutropenia."* **[3]**

> *"Full implementation of risk stratified management of NS, and a further reduction in treatment duration, was made possible by the rapid validation by the York team ……This enabled a newly agreed national strategy to be delivered through the CCLG."* **[2]**

Data from CCLG audits comparing length of stay and antibiotic use in 2017 and preliminary data from 2020, combined with NHS National Cost Collection data illustrates that implementation of risk stratified management has resulted in a substantial cost saving for the NHS. The proportion of NS episodes discharged within 24 hours increased from 0% to 27%, and average inpatient stay reduced from 3.5 days to 1.8 days for those who were hospitalised. Given costs of GBP997 per inpatient bed day and GBP538 for day case management, this generates savings of GBP2,010 per episode. A further small saving of GBP21 per episode accrues from low risk patients switching from IV to oral antibiotics. Using 2020 estimated annual incidence of 3,011 NS episodes, this equates to freeing up 5,703 bed days and reducing NHS costs by GBP6,115,563 per year **[4][5]**.

(2) Impact on international clinical practice:
York research has also directly informed and "*been instrumental to the development and completion*" **[5]** of international guidelines, which have in turn changed practice and delivered international impact as the clinical lead/corresponding author of the International Society of Paediatric Oncology guidelines notes:

> *"… research on the management of fever and neutropenia in children and young people being treated for cancer undertaken by the team at the Centre for Reviews and Dissemination at the University of York was an important source of evidence for the international clinical guidelines that were produced by an international panel of pediatric oncology experts, including Dr Bob Phillips. The guidelines were subsequently adopted by The International Society of Paediatric Oncology (SIOP). During development, the York team's published and not yet published research … was particularly important in informing recommendations about the initial management of FN. The guidelines … have since been adopted by the American Society of Pediatric Hematology/Oncology, the Pediatric Oncology Group of Ontario, the American Society of Clinical Oncology, C17 Council (an organisation including institutionally appointed heads of the 16 paediatric hematology, oncology and stem cell transplant programmes across Canada), the Multinational Association of Supportive Care in Cancer (MASCC) and Children's Oncology Group (COG).* **[5]**

Guideline recommendations are now included in every new anti-cancer study undertaken across the North American COG network and widely within Europe **[5]**.

Studies carried out in children's hospitals in the US have also reported benefits arising from guideline-congruent low risk management. In Oklahoma costs of NS management in low risk patients were halved: "*The mean total cost of an LRFN episode was $12,500 per patient pre implementation and $6168 post implementation, a decrease of $6332 (51%) per patient".* In Massachusetts *"40% of [NS] episodes were defined as low risk and managed either entirely in the outpatient setting ...or with a step down strategy involving a very brief inpatient stay"* and in Missouri over 60% of CYP presenting with NS were discharged early ("*188/299 FN admissions*"). The Missouri study noted that "*by reducing the overall length of stay in a subset of patients, early discharge can improve quality of life and reduce costs. This practice may also benefit patients in terms of safety by decreasing the risk of hospital-acquired infections and avoiding prolonged antibiotic exposure that leads to resistant bacterial and fungal infections"* **[6]**.

The Melbourne based PICNICC-Australia team demonstrated that adopting risk stratified management saved *"290 in-hospital bed days in 18 months"* and reported that with in-hospital management of paediatric low-risk NS costing AUD2,200 per day and home-based NS care approximately AUD830 per day*, "the cost benefit …is likely to be substantial*" and that the *"program is currently being scaled nationally, thereby increasing the clinical, economic and quality of life impact of this model of care"* **[7]**.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. **NICE CLINICAL GUIDELINES:** NICE guideline (CG151) highlighting references to underpinning York research and a screenshot from NICE webpages confirming that the guidance was considered up to date in January 2020.
2. **AUDITS ILLUSTRATING UK CHANGING PRACTICE:** Letter from the National Children's Cancer and Leukemia Group (CCLG) CEO (25/09/2020) providing information on audit and changing UK practice, listing CCLG audit references, and also commenting on York role in the development of national strategy for responding to COVID-19.
3. **IMPACT ON NHS MANAGEMENT DURING SARS-CoV2/COVID19:** Letter from the CCLG Chair (13/10/2020) describing how underpinning York research, including rapid review work undertaken in March 2020, along with research led implementation, contributed to minimising NS hospitalisation as a key component of the national strategy for managing paediatric oncology services during COVID-19. It also comments on changing UK practice.
4. **NHS SAVINGS:** Excel calculator used to estimate NHS savings arising from increased implementation of risk stratified management, between 2017 and 2020. These calculations can be confirmed by an independent senior health economist.
5. **INTERNATIONAL CLINICAL GUIDELINES:** Letters from the clinical lead/ corresponding author of the international/SIOP guidelines (07/12/2020) and from the Chair of the immunocompromised child section of the German Society of Pediatric Infectious Diseases Infection/ co-chair of the SIOP supportive care working group (11/12/2020), confirming that York research directly informed guideline development; also listing the many international groups that have adopted the guideline. Two journal publications (DOI: 10.1200/JCO.2016.71.7017, DOI: 10.1200/JCO.2012.42.7161) of the guidelines are also included and marked up to indicate references and links to York underpinning research.
6. **USA RESOURCE SAVINGS:** Three peer reviewed publications of US studies that evaluated resource and satisfaction aspects of implementing guideline congruent (international SIOP) management of CYP with low risk NS: Oklahoma: DOI: 10.1097/MPH.0000000000001084; Massachusetts: DOI: 10.1002/pbc.27679; Missouri DOI: 10.1002/pbc.26072.
7. **AUSTRALIAN COST SAVINGS NATIONAL IMPLEMENTATION**: Peer reviewed publication describing savings made by implementing a risk stratified approach in Melbourne and noting national roll out of risk stratified management DOI: 10.1007/s00520-020-05654-z.