The project title was changed to:

Project Description - as in your original application

This grant will enable us to replace standard, highly invasive blood-taking techniques with innovative microsampling techniques (measuring antibiotic concentrations from a drop of blood) taken as part of clinical practice. We will perform a clinical study to characterise the behaviour of antibiotics that are commonly used in children. We can then develop antibiotic doses that are personalised for the individual circumstances of each child. This research will ensure optimised treatment of infections resulting in better patient outcomes and potentially, a reduction in the emergence of antibiotic resistant 'superbugs'. This innovation may enable clinical care and research for sick children.

ABOUT YOUR PROJECT

You had the opportunity to list up to five project goals in your application. Here are the project goals you listed:

Goal 1

Validate microsampling techniques into clinical practice for the optimisation of antibiotic dosing in infants and children.

KPI/Timeline 1

1. Four trained laboratory staff using robotic sample processing
2. Three trained clinical collaborators in using microsampling
3. Three scholarly publications describing the validation of the analysis of antibiotics (gentamicin, cefazolin and ampicillin) using microsampling.
4. Future collaborations for the application of microsampling in clinical practice in infants and children

Goal 2

Characterise the behaviour of antibiotics in infants and children with severe infection and establish robust, evidence-based antibiotic doses.

KPI/Timeline 2

1. Four students trained in population pharmacokinetic modelling workshops
2. Three scholarly publications describing the results of population pharmacokinetic studies and Monte Carlo dosing simulations, of key antibiotics - gentamicin, ampicillin and cefazolin - in critically ill children.
3. Future collaborations for population pharmacokinetic modelling of antibiotic dosing

Goal 3

KPI/Timeline 3

Goal 4

KPI/Timeline 4

Goal 5

KPI/Timeline 5

1. Did the project achieve its goals?

Address each of the above listed goals separately. If relevant, please provide quantitative data about your project. For example: How many people were involved in the project? How many workshops were delivered? Etc.

Goal 1:

We have validated and published five methods for the analysis of antibiotics using microsamples with an additional two methods that have completed validation and are in the process of manuscript preparation. A further five antibiotics are in the final stages of validation. The results of the clinical bridging studies in adults (performed prior to implementation in infants and children) are in the process of statistical analysis for publication for one antibiotic (with one remaining patient required for total recruitment). Two other clinical bridging studies are underway with recruitment progressing. One antibiotic was delayed due to world-wide supply shortages in 2017.

KPIs:

1. One PhD student, three laboratory staff and one clinical collaborator have been trained to use the robotic equipment used for sample processing.

2. Six publications have resulted from the work undertaken on microsampling.

3. We have three new projects with new clinical collaborators:
(i) USyd Professor Greg Fox (respiratory physician) and Clinical collaborator Dr Andrew Burke (infectious disease expert
(ii) Pathology Queensland
(iii) Dr Mark Davies (neonatologist) and Dr Adam Irwin (paediatric infectious disease expert)

Goal 2:

This element of the project has been delayed but recruitment for this study is due to commence in July 2018. During these delays, we have successfully obtained funding for this work

KPI:

1. CI Parker held weekly population pharmacokinetic modelling workshops. These have been attended by clinical collaborators, PhD students, research scientists, and visiting scholars with up to 10 attendees.

2. CI Parker has two publications with population pharmacokinetic model with Monte Carlo simulations reflecting the ongoing work in this area.

3. Future collaborations for population pharmacokinetic modelling, including:
a. Paediatric surgeon?s Dr Nelson Alphonso and Dr Prem Venugopal at Lady Cilento Children?s Hospital
b. Anaesthetist Dr Rochelle Ryan at Sunshine Coast Hospital

2. What did you learn?

For example: improvement areas, reasons for success or challenges, unanticipated outcomes, ideas for how you will apply learnings to future projects.

A key area of learning is the expectation for patient recruitment. Initially it was envisaged that the clinical bridging study would have completed recruitment in 6 months. However, it remains at the recruitment stage, with 48% of patients recruited after commencing over 2 years ago. Some of these delays are due to worldwide supply shortages of two antibiotics. To avoid future delays, we are incorporating the bridging study into the children?s study, by collecting paired samples obtained through routine clinical care.

For the validation of microsampling we have identified an important feature that limits the application of dried blood spots to clinical practice. Our finding was that the recovery of an antibiotic from dried blood spots changes with time, meaning that concentrations obtained when dried blood spots are freshly prepared are different to older samples. This has significant impact on the reliability of data obtained. We have published this finding. The

outcome of this work has been incorporated into our rigorous validation testing program, such that we test for changes to recovery across time for all dried microsamples.

3. Was the project completed within the proposed timeframe? Maximum 30 words.

No, the clinical bridging study is still recruiting. The clinical study in critically ill infants and children will commence in July 2018.

4. Did you make any changes? If so, why?

i.e. changes to the original proposal, reasons for them and how they affected the project.

Yes, from our original submission we changed the antibiotics we were investigating. There were two reasons for the changes. (1) The antibiotics failed to meet acceptance criteria in the laboratory for the application of microsampling (as defined by international regulatory agencies) and (2) to improve the opportunity for recruitment during the clinical bridging study. We moved ahead with the antibiotics vancomycin, meropenem and piperacillin-tazobactam. These antibiotics met the validation criteria and are heavily used within the ICU. Unfortunately, both meropenem and piperacillin-tazobactam have experienced world-wide supply shortages in the last 18 months. These shortages meant we were unable to recruit for these antibiotics. The study for vancomycin has recruited over 90% of patients. This has led to our revision of the study in critically ill infants and children and we have expanded our antibiotic range to improve opportunities for recruitment.

5. In your application you identified the following (up to 5) long term outcomes:

Note: if you applied prior to June 2015, we have selected (up to five) outcomes based on goals stated in your application.

Improved health and wellbeing--
Promotion/dissemination of best practice/new knowledge--
Improved operational capacity/capability--
Improved skill base--

5a. Did you collect any measurements on long-term outcome 1?

If so, explain. If not, explain why not/future plans.

Improved health and well-being: This continues to be our goal for improved treatment of severe infection in critically ill infants and children. Our future plans are to measure the uptake of recommended doses into clinical practice, for microsampling uptake into therapeutic drug monitoring(TDM). These targets remain as measures of our success. We have established a project with Pathology Queensland to improve the likelihood of microsampling being used for TDM.

5b. Did you collect any measurements on long-term outcome 2?

If so, explain. If not, explain why not/future plans.

In 2017 we held a Symposium on Drug Dosing: Innovation in Microsampling and this will be held again on 20 Sept 2018. This event is an opportunity to present and promote our knowledge to clinicians, bioanalysts, pharmacologists, and research scientists. It was well received in 2017, with 39 attendees and 6 sites joined via videoconferencing and included visiting faculty from UWA and RMIT and industry representatives. For our event in 2018 we have three international faculty members.

5c. Did you collect any measurements on long-term outcome 3?

If so, explain. If not, explain why not/future plans.

This project has resulted in us successfully obtaining an NHMRC Early Career Fellowship for CI Parker and we have project funding from the Children?s Hospital Foundation for 2018-19. We have applied for funding for 2019-2021 from the NHMRC and Perpetual Ramaciotti as project grants. Furthermore, we have been successful in

obtaining two grants for microsampling projects ? from the University of Queensland and Royal Brisbane Hospital Foundation. We have also established key collaborations with infectious disease experts, pathologists and neonatologists.

5d. Did you collect any measurements on long-term outcome 4?
If so, explain. If not, explain why not/future plans.

Improved skill base: From this project CI Parker has published as first and senior author six publications for the application of microsampling in a clinical environment. She has also published two population PK studies. Two PhD students have been able to progress their research projects based on the work within this project. The work that has been achieved is likely to lead to an additional 12 publications in the next 12 months.

5e. Did you collect any measurements on long-term outcome 5?
If so, explain. If not, explain why not/future plans.

6. Were you able to leverage Foundation's funding to gain other support?
e.g. such as grants from other sources, on-going funding, other forms of support, or other benefits.

Yes

Please enter the $ amount leveraged from government sources.
322952

Please enter the $ amount leveraged from non-government sources.
340961

If applicable, please state the organisation(s) and amount(s). Maximum 255 characters.
NHMRC ECR Fellowship $322952 Childrens Hospital Foundation $295445 Royal Brisbane Hospital Foundation $79500 UQ $39900 Mary McConell Grant (Childrens Hospital Foundation) $45396

Next steps

FINAL REPORT

7. Will the project continue beyond the grant period?
Yes

If continuing, please outline the future of the project.
If you received a Medical Research grant from the Foundation please outline where you are in the invention disclosure process. Do you plan to file patents? Is there evidence of commercial engagement and/or industry collaboration? To which NHMRC/ARC round will you apply?
Yes. The study at the Children?s Hospital Foundation will commence recruitment in July 2018.

Publications on the application of microsampling to the clinical environment have been cited by industry: hospitals, pharmaceutical companies, and regulatory authorities. This includes hospitals in Greece, Hungary, USA, UK; AstraZeneca, Merck Co., Johnson & Johnson, GlaxoSmithKline; and the Food and Drug Administration.

We have applied for funding for 2019-2021 from the NHMRC and Perpetual Ramaciotti as project grants.

8. Have the project outcomes already been shared with others? If so, how?
e.g., newsletters, conference presentations, public launch, publication of report

Yes: In 2017 we held a Symposium on Drug Dosing: Innovation in Microsampling ? this was promoted with newsletters and on social media, including videoing of the presentations available on YouTube. In 2017 the results have been presented at Australian Society of Clinical and Experimental Pharmacologists and Toxicologists,

Antimicrobial Optimisation Workshop, Queensland Mass Spectrometry Symposium and Pathology Queensland Grand Rounds. Publications have been promoted on social media.

FEEDBACK

Do you have any suggestions of ways in which we could improve our processes? Any general comments?
NA

Financial statement

FINANCIAL STATEMENT

Please attach a statement of **total project income and expenditure** (not just the expenditure of the Foundation's grant). It must account for the total income and expenditure of the project and it **must** be signed and dated by the relevant authorised person (e.g. CEO, CFO, Research/Grants Management Accountant) with itemisation of:

- the amount received from The Ian Potter Foundation
- the cash financial contribution received from your organisation
- other funding sources and amounts received from them
- amounts expended and
- the balance (if any) remaining at date of this report.

Note: You should comment on any significant changes in budget items from the original budget proposed.

In order for us to get a complete understanding of how your project went, we need a financial report in the same format as the budget you submitted in your application. Please include in the income and expenditure sections columns titled *"estimated"* **and** *"actual"* (as in the report template).

If you used your own budget template when you applied, please use the same cost headings, adding additional headings and rows to account for unanticipated costs.

If you used the Foundation's budget template when you applied you may like to use the IPF FINANCIAL REPORT TEMPLATE. You should add additional headings and rows where necessary in order to provide as complete an itemised financial report as possible.

Print a copy of the completed financial statement and arrange for it to be **signed and dated** by the relevant authorised person (see above). Then scan it and upload it as an attachment.

Financial Report attachment

019485_AS AT_2018-05-31 FS.pdf

Attachments

Title	File Name
Photo / image 1	Screen Shot 2018-06-29 at 9.22.55 AM.png
Photo / image 2	Screen Shot 2018-06-29 at 9.22.19 AM.png
Photo / image 3	Screen Shot 2018-06-29 at 9.21.50 AM.png

Report / newsletter / other 1