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Grant writing course

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THE UNIVERSITY of EDINBURGH

BBSRC bioscience for the future

Introductions

- Our aims
- Your aims
- Structure of the course
- Please interrupt & ask questions
- Please let us know how it can be improved

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Overview of the funding process

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Sources of funding for research

- QR (Quality of Research) block grant from the Higher Education Funding Council (in our case the Scottish Funding Council, SFC)
  - Informed by Research Excellence Framework (REF) assessments
  - Quanta of funding to University per area/researcher based on output
- Research Councils
- Government departments & agencies
- Charities, academies, societies & levy bodies
- Industry contracts

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Research Councils

RESEARCH COUNCILS UK

Seven major research councils in the UK, organised under RCUK:

- Arts & Humanities Research Council (AHRC)
- Biotechnology & Biological Sciences Research Council (BBSRC)
- Economic & Social Research Council (ESRC)
- Engineering & Physical Sciences Research Council (EPSRC)
- Medical Research Council (MRC)
- Natural Environment Research Council (NERC)
- Science and Technology Facilities Council (STFC)

See: http://www.rcuk.ac.uk/international/Offices/OfficeintheUS/Pages/TheUKResCouncils.aspx

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Research Councils

- Receive grants from Department of Business, Innovation & Skills (BIS) via government Comprehensive Spending Review
- Allocate funding via strategic alliances & competitive awards for specific projects (‘dual support’ model)
- BBSRC invest in The Roslin Institute both via core strategic grants (Integrated Strategic Programmes, ISPs) & competitive awards
- Differ in remit but over-lap in some areas
- All publish & review their strategic priorities

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Government Departments & Agencies

- Department for the Environment, Food & Rural Affairs (DEFRA)
- Technology Strategy Board (TSB)
- Food Standards Agency (FSA)
- Ministry of Defence (MoD)
- National Health Service (NHS) & National Institute for Health Research (NIHR)
- Department for International Development (DfID)
- May publish own research requirements or co-fund initiatives with RCUK
- Research tends to be more applied

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Charities, Academies, Societies & Levy Bodies

- Vary hugely in size & remit
- Funding may be driven by
  - Revenue & Investments (e.g. Wellcome Trust)
  - Philanthropy (e.g. Gates Foundation)
  - Donations (e.g. Cancer Research UK)
  - Publishing & subscription revenue (e.g. Royal Society)
  - Industry levies (e.g. BPEX, HBLB)
  - Interests in specific diseases
  - Some co-fund research with RCUK for specific activities (e.g. NC3Rs)
- Often fund doctoral training & fellowships

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Sources of overseas funding

- The European Commission is a major funder
- Funds consortium projects & networks but also Marie Curie studentships & fellowships
- Complex administration & funding allocation can be political
- May be eligible for schemes in other countries if expertise or facilities lacking locally (e.g. NIH)
- Increasing number of partnering initiatives to build alliances via co-funding (e.g. UK-US, -China, -Brazil, -India)

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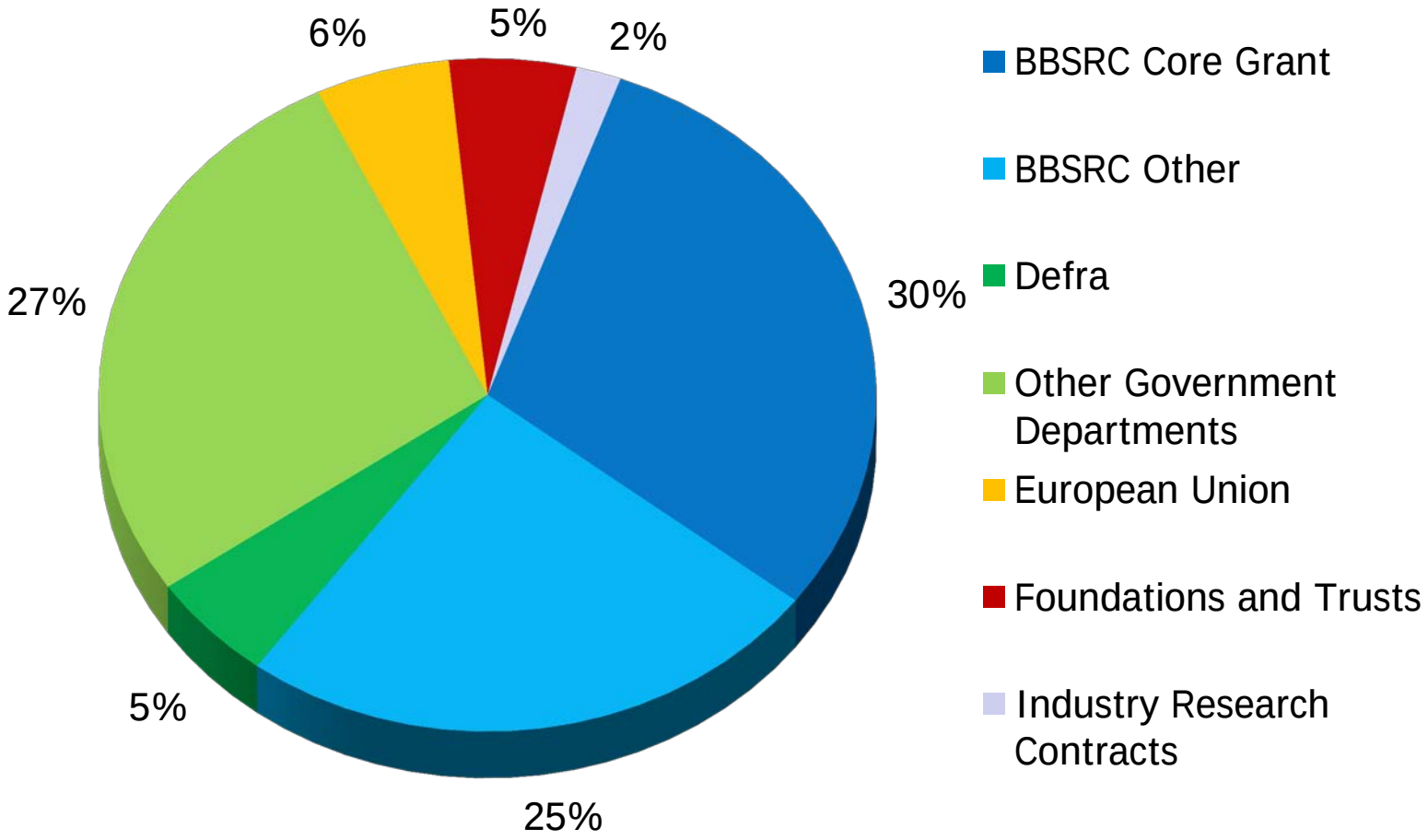
Sources of funding at The Roslin Institute 2012-2013



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Funding schemes

- Response-mode
  - Open (though deadlines usually apply - often 4 rounds/year)
  - Can address any subject within strategic remit of funder (check!)
- Specific call
  - Some funders publish annual research requirements
  - Initiatives may be used to attract proposals or collaborations in specific areas
- Keep informed at http://intranet.roslin.ed.ac.uk/intranet/grants/

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Funding schemes

- Project grants for postdoctoral &/or technical posts (small to sLoLa)
- Ph.D studentships
- Fellowships (to applicant)
- New Investigator project grants
- Industry-linked projects (e.g. CASE, IPA, LINK)
- Joint government funding (e.g. GPA, MoD)
- Follow-on funding for translation of research
- Pump-priming initiatives

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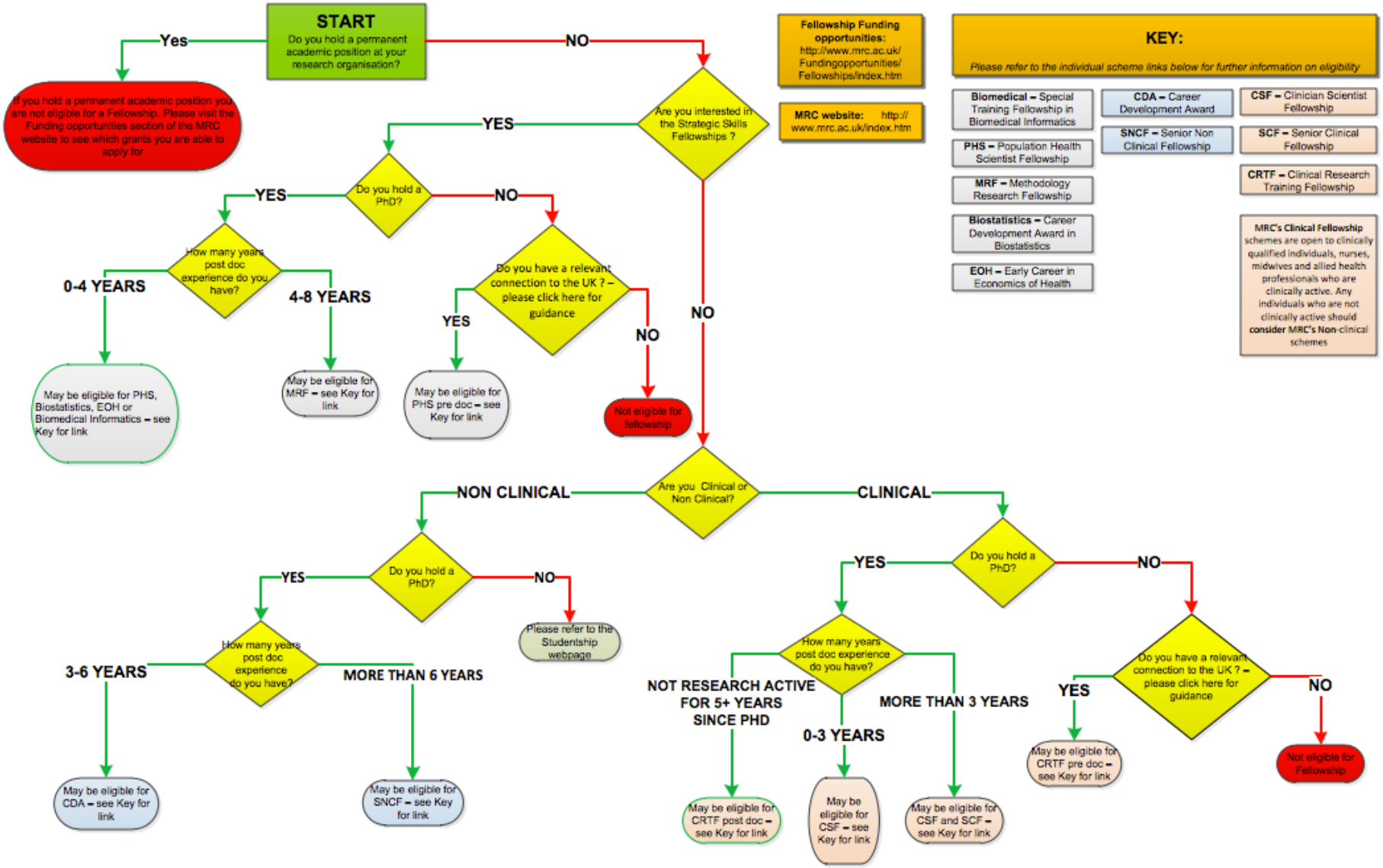
Fellowship schemes

- Prestigious but highly competitive
- A variety of UK-based sources
  e.g. BBSRC, MRC, Royal Society, Wellcome Trust, Universities
- Aimed at various levels of experience
- Fixed interval, but may be subject to renewal
- Often strict eligibility criteria (principally years post-Ph.D)
- Unwritten rules for shortlisting
- Favour candidates with proven publication records, evidence of independence & moving between institutions

Fellowship Eligibility Checker



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If in doubt, ask the funder

Fellowships versus grant applications

- For all proposals, project, people & place are scrutinised
- Fellowship panels arguably place emphasis on potential (person > project) & likely to require an interview
- Grant panels arguably place emphasis on project > people & typically do not interview
- Grants can involve co-investigators & consortia, but fellowships are awarded to individuals
- Think carefully about skills required for the project & how to separate yourself (or benefit from) mentors

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Process from receipt to decision

- Applications screened for compliance with eligibility & format rules
- Sent for peer-review
- Referee reports returned, usually with the right-to-reply
- Some funders ask for scores before panel meeting & triage
- Designated Panel Member(s) assigned to review proposal & reports in detail & present to panel
- Applications scored by all panel members then ranked
- Scores may be raised if project involves co-funding (e.g. IPA, GPA, LINK), new investigator or addresses a strategic priority
- Cut-off applied (sometimes after budget trimming) & decisions sent

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It all starts with your idea..!

- Is your idea aligned to the strategic priorities of the funder(s)?
- Does it address a significant problem, given finite funding?
- Is the funding scheme & level of support proposed realistic?
- Might industry or other funders be interested?
- Stress-test the concept & approach with colleagues &/or collaborators

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Where do ideas come from..?

- May be an extension of ongoing work
- Collaboration
- Publications (read widely...)
- Symposia & seminars (network effectively...)
- Discussion with colleagues
- Call from funder for projects in a specific area
- It takes time to understand funder priorities & how best to target them (seek advice...)

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The Application

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Before you start writing...

- Review sources of funding & check eligibility
- Are the required expertise, facilities & materials available?
- Map out the plan & approaches
- Flow charts, spider diagrams & Gantt charts may help
- Does the project overlap significantly with other projects in the funders portfolio or the host institution (e.g. via ISPGs)?
- Would preliminary data strengthen the application?
- Network effectively in your research community - they'll review it..!

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Consider the funders perspective

- What will be the key outcomes & do they address our priorities?
- Will the data obtained be an incremental extension of existing knowledge or a novel & significant advance?
- Is the project merely descriptive or could the knowledge be applied?
- Is the balance of risk & return appropriate?
- Does it offer value-for-money?
- Will it generate ‘impact’ that drives research council funding?
- Is it founded on preliminary data & proven track record(s)?

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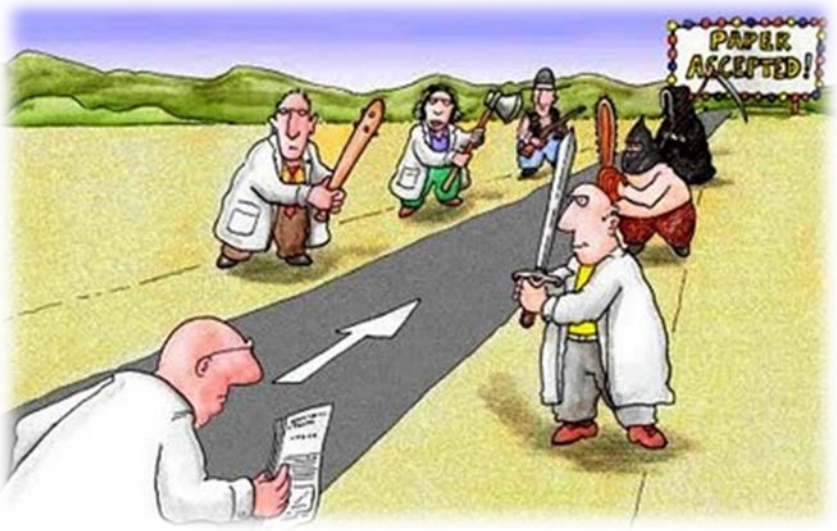
Be mindful of the review process



- The panel may have over a hundred applications to consider
- Your grant will typically be introduced by 2 panel members
- She/he may handle 5-10 applications, including the Case for Support, peripheral sections, CVs, referees comments & your responses
- They will have just a few minutes to explain your project & advocate for it
- The purpose, aims & expected outputs should be intelligible to a broad audience as not all panel members will be an expert in your field
- Seek experience as a reviewer, you'll learn a lot

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Know what referees are looking for (& asked to comment on)

- Scientific excellence
  - Clarity of hypothesis, aims & objectives
  - Strengths & weaknesses of experimental design
  - Feasibility of work given record of the applicant(s)
- Strategic relevance
  - To funders strategic priorities
  - To industry & other stakeholders
- Economic & societal impact of the proposed study
- Timeliness & promise
- Value for money
- Staff training potential

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Some guiding principles

- Attention to detail is important. A poorly written proposal full of errors will convey a lack of care
- Follow guidance notes & remit of call. Rules on font & format are enforced
- Strive to be concise & precise. Waffle is infuriating if you have 10 grants to review
- Use a clear engaging style that conveys excitement but does not promise too much/little, overstate the problem or mask challenges
- Make use of diagrams or images that help to tell the story. They break up the text, add interest & can say a thousand words
- Use emphasis (bold or italics) to draw attention to salient aspects

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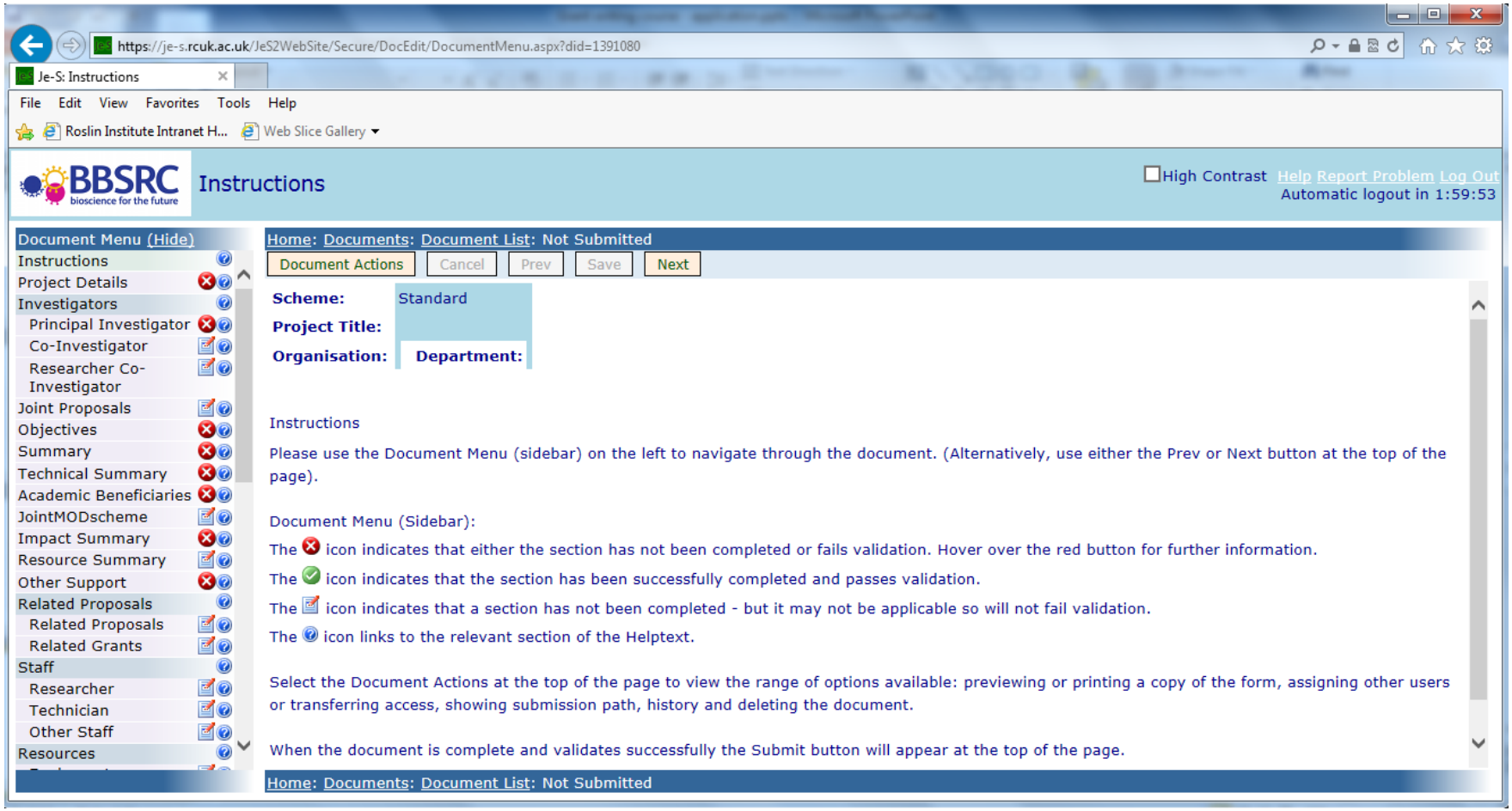
RCUK use a common on-line submission system (Je-S)

https://je-s.rcuk.ac.uk/



Registration performed by host institution to confirm eligibility

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Title & timescale

- Use a short informative title
- Avoid abbreviations & jargon
- Make it accessible to a broad audience
- In some cases it is useful to convey the purpose or expected outcome

TraDIS analysis of *S. enterica* serovar Typhimurium in *Gallus gallus*, *Bos taurus* & *Sus scrofa*

vs.

Global assignment of roles for *Salmonella* genes in food-producing animals

- Be realistic about the timescale. It often takes 9-12 months from submission to appointment
- Is the project duration realistic given the objectives & resources requested? Not all projects need to follow a 3 year formula

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Applicants

- Be honest & realistic about the expertise required to deliver the project
- Absence of a productive record in the field of study will raise concern
- Submission with an experienced co-investigator can lend confidence
- Working ‘under the wing’ of a colleague can instil valuable training
- PDRAs may be able to apply as ‘Researcher Co-Investigator’
- A joint project that integrates the expertise of colleagues may be needed where no single investigator has the requisite skills or record

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Collaborators, partners & sub-contracts

- Joint applications can be submitted, where collaborators submit separate costs & act as local PI
- A lead PI is required
- Contribution of collaborators must be clear, necessary & justified
- Collaboration should build strength to your proposal, for example providing access to facilities, expertise or materials lacking locally
- Where only modest external input is needed partners can be named & linked via a signed letter of support
- Where only a service is required (e.g. sequencing, animal trial) a sub-contract may be appropriate

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Objectives

- One of the first sections to be read, so make a good impression
- A short preface to provide context may help
- Make objectives clear & intelligible to non-specialists
- Order & wording should mirror those in the Case for Support
- Avoid too much sub-division of tasks & focus on ‘higher level’ aims
- Consider objectives that are SMART (Specific, Measurable, Achievable, Realistic and Time-limited)
- Ensure they are logically ordered & avoid inter-dependent objectives (i.e. where delivery of objectives 2-5 relies on a crucial reagent to be made in objective 1)

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Lay summary

- Take it seriously..!
- Plain English is often the best & simplest way to convey the purpose of your study
- Some panel members will not be specialists in your field & may only read this section & your objectives
- Genuinely pitch this at the lay public & avoid technical jargon
- Invite lay people to review & comment
- Set the project in context & explain why the project is needed and how the data can be used

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Technical summary

- Entered into form separately from the Case for Support & typically read first
- Use a style akin to that used in the abstract of a scientific paper
- Pitch at the level of experts in your discipline
- Don’t assume they’ll know the background to your specific area
- Succinctly introduce the problem, approach & expected outcomes
- Technical & lay summaries are made available to the public

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Case for Support - Track Record & Previous Research (1)

- Your chance to shine..!
- Introduce your role & brief history, but don't write a CV (a separate ~2 page CV is needed for all participants)
- What is unique or innovative about your approach?
- Concisely introduce your role in work leading up to the proposal, identifying your publications & any previous funding
- Don't write a general literature review - convey why you, your team & your organisation are the best placed to conduct the study
- State impacts of your work on academia or stakeholders (even if the award was to your manager) - it will lend confidence that you can deliver
- Use separate paragraphs for named collaborators & make clear what they add

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Case for Support - Track Record & Previous Research (2)

- Consider a section that describes the research environment & synergy with ongoing activities &/or alignment to funder priorities
- Especially important if the project ‘adds value’ to other activities
- Hypotheses, objectives & plans should not be introduced in any detail
- Don’t waste space listing references if they can be found in CVs of the applicants or the Case for Support itself

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Case for Support

- The key part on which all proposals stand or fall..!
- Standard ‘response-mode’ RCUK proposals span 6 pages
- In general comprises
  - Introduction
  - Preliminary data
  - Hypothesis &/or aims
  - Programme & Methodology
  - Concluding remarks

- Experimental plans described under each objective
- It may be helpful to specify milestones & deliverables
- A 1 page Gantt Chart that identifies tasks & plans for their delivery over time or locations is permitted
- Don’t be bound be convention, but you must address these aspects

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Introduction

- State an overarching problem or need
- Provide enough information to set the proposed research into context
- Within this area, identify gaps in knowledge & research priorities
- Don’t write a comprehensive literature review, expert reviewers will know the background anyway
- Use figures or diagrams to engage reader interest (nothing is worse than 6 pages of continuous block text)
- Use transparent & accurate referencing to honestly describe the state of knowledge & the contributions of others (who may review it)

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Preliminary data

Part 2: Case for support

Introduction. Human non-typhoidal salmonellosis is frequently acquired from food-producing animals and an estimated 93.8 million cases and 155,000 deaths occur worldwide each year[1]. Cattle are a significant reservoir of such infections owing to the ability of selected *Salmonella enterica* serovars to persist in the bovine gastrointestinal and lymphatic systems (reviewed in[2]). Though the intestines and draining mesenteric lymph nodes (MLN) typically do not enter the food chain, peripheral lymph nodes and associated adipose tissue are frequently incorporated into ground beef for human consumption. The prevalence of *Salmonella* in bovine peripheral lymph nodes varies with anatomical location[3] and farm[4], but *Salmonella* has been detected in the superficial cervical nodes of up to 88% of beef carcasses[5]. Typing by pulsed-field gel electrophoresis has indicated that the lymph nodes and hide are key sources of *Salmonella* found in ground beef, with up to 1.7% of ground beef samples testing positive from a cohort of cattle where 18% of superficial cervical nodes were contaminated[6]. Elimination of peripheral lymph nodes is not feasible on the scale of modern beef production owing to their number, small size and inaccessibility. As a consequence, significant outbreaks of human salmonellosis caused by ground beef have occurred, for example due to multi-drug resistant serovar Typhimurium and Newport strains[7]. Tracing of *Salmonella* outbreaks to ground beef has profound implications for producers owing to product recall, compensation and lost revenue. *Salmonella* can also exert substantial welfare and productivity costs in cattle. For example, *S.* Typhimurium is a significant cause of bovine diarrhoea whereas *S.* Dublin causes severe typhoid-like illness and abortion[8].

We have developed unique surgical and challenge models to unravel the basis of bacterial persistence, pathogenesis and clearance during bovine salmonellosis. In age-matched calves dosed by the oral route *S.* Dublin SD3246 causes typhoid-like systemic disease, *S.* Typhimurium ST4/74 causes acute enteritis whereas *S. Gallinarum* SG9 is cleared in the absence of overt pathology[9]. These distinct outcomes are not associated with the ability of the strains to invade the intestinal mucosa or the magnitude of inflammatory and secretory responses in ileal loops[9]. The nature and consequences of the interactions between such strains and host cells are ill-defined, but each appears to penetrate the epithelium via ileal microfold (M)-cells and enterocytes then transit rapidly to lamina propria MHC II$^+$ cells[10]. All three strains appear in ileal MLN in comparable numbers 12-24 h after infection, but at later times *S.* Dublin SD3246 persists in MLN whereas *S. Gallinarum* SG9 is cleared[9,10]. Moreover, by cannulation of efferent lymph vessels in the distal ileum we observed that SD3246 leaves MLN in a cell-free niche in significantly greater numbers than SG9 following oral dosing or instillation of bacteria into the distal ileal loop[9,10]. MLN therefore appear to restrict systemic translocation of selected serovars from the bovine intestines, consistent with their role in limiting acute and relapsing typhoid after oral *S.* Typhimurium infection in mice[11,12].

By using signature-tagged *S.* Dublin mutants we observed that visceral organs such as the liver are seeded by the same clones, in the same proportions, as migrating via efferent lymph[10] (Fig. 1).

Fig. 1. Analysis of the mode & genetics of systemic translocation of *S.* Dublin in cattle. An efferent lymph vessel exiting MLN serving the distal ileal loop was cannulated under terminal anaesthesia (left panels). The loop was inoculated with a pool of signature-tagged SD3246 mutants to assign the role of 30 sensor kinases in transit through varied anatomical niches relative to the wild-type strain (right panels). The intensity of the spots reflects the relative abundance of the cognate mutants.

We have used this method to simultaneously assign the role of tens of virulence-associated loci[10], *S.* Dublin-specific genes[13] and sensory systems[14] in mucosal invasion, spread to MLN and migration via efferent lymph. Our data indicate that lymphatic translocation is highly relevant in dissemination of *Salmonella* from the bovine gut to other tissues. *S.* Dublin was rarely detected in venous blood serving the bovine distal ileum early after infection[9,10], in contrast to observations in the murine typhoid model where CD18$^+$ phagocytes transport *S.* Typhimurium to the blood[15].

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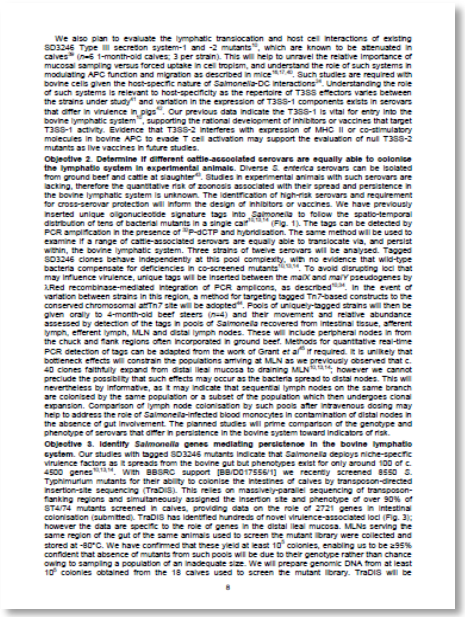
vs.



We also plan to evaluate the lymphatic translocation and host cell interactions of existing SD3246 Type III secretion system-1 and -2 mutants[16], which are known to be attenuated in calves[16] (n=6 1-month-old calves; 3 per strain). This will help to unravel the relative importance of mucosal sampling versus forced uptake in cell tropism, and understand the role of such systems in modulating APC function and migration as described in mice[16,17,18]. Such studies are required with bovine cells given the host-specific nature of *Salmonella*-DC interactions[19]. Understanding the role of such systems is relevant to host-specificity as the repertoire of T3SS effectors varies between the strains under study[20] and variation in the expression of T3SS-1 components exists in serovars that differ in virulence in pigs[21]. Our previous data indicate the T3SS-1 is vital for entry into the bovine lymphatic system[10], supporting the rational development of inhibitors or vaccines that target T3SS-1 activity. Evidence that T3SS-2 interferes with expression of MHC II or co-stimulatory molecules in bovine APC to evade T cell activation may support the evaluation of null T3SS-2 mutants as live vaccines in future studies.

Objective 2. Determine if different cattle-associated serovars are equally able to colonise the lymphatic system in experimental animals. Diverse *S. enterica* serovars can be isolated from ground beef and cattle at slaughter[22]. Studies in experimental animals with such serovars are lacking, therefore the quantitative risk of zoonosis associated with their spread and persistence in the bovine lymphatic system is unknown. The identification of high-risk serovars and requirement for cross-serovar protection will inform the design of inhibitors or vaccines. We have previously inserted unique oligonucleotide signature tags into *Salmonella* to follow the spatio-temporal distribution of tens of bacterial mutants in a single calf[10,13,14] (Fig. 1). The tags can be detected by PCR amplification in the presence of ^{32}P-dCTP and hybridisation. The same method will be used to examine if a range of cattle-associated serovars are equally able to translocate via, and persist within, the bovine lymphatic system. Three strains of twelve serovars will be analysed. Tagged SD3246 clones behave independently at this pool complexity, with no evidence that wild-type bacteria compensate for deficiencies in co-screened mutants[10,16,18]. To avoid disrupting loci that may influence virulence, unique tags will be inserted between the *malX* and *malY* pseudogenes by λRed recombinase-mediated integration of PCR amplicons, as described[10,23]. In the event of variation between strains in this region, a method for targeting tagged Tn*7*-based constructs to the conserved chromosomal *attTn7* site will be adopted[24]. Pools of uniquely-tagged strains will then be given orally to 4-month-old beef steers (n=4) and their movement and relative abundance assessed by detection of the tags in pools of *Salmonella* recovered from intestinal tissue, afferent lymph, efferent lymph, MLN and distal lymph nodes. These will include peripheral nodes in from the chuck and flank regions often incorporated in ground beef. Methods for quantitative real-time PCR detection of tags can be adapted from the work of Grant *et al*[25] if required. It is unlikely that bottleneck effects will constrain the populations arriving at MLN as we previously observed that c. 40 clones faithfully expand from distal ileal mucosa to draining MLN[10,13,14]; however we cannot preclude the possibility that such effects may occur as the bacteria spread to distal nodes. This will nevertheless by informative, as it may indicate that sequential lymph nodes on the same branch are colonised by the same population or a subset of the population which then undergoes clonal expansion. Comparison of lymph node colonisation by such pools after intravenous dosing may help to address the role of *Salmonella*-infected blood monocytes in contamination of distal nodes in the absence of gut involvement. The planned studies will prime comparison of the genotype and phenotype of serovars that differ in persistence in the bovine system toward indicators of risk.

Objective 3. Identify *Salmonella* genes mediating persistence in the bovine lymphatic system. Our studies with tagged SD3246 mutants indicate that *Salmonella* deploys niche-specific virulence factors as it spreads from the bovine gut but phenotypes exist for only around 100 of c. 4500 genes[10,13,14]. With BBSRC support [BB/D017556/1] we recently screened 8550 *S.* Typhimurium mutants for their ability to colonise the intestines of calves by transposon-directed insertion-site sequencing (TraDIS). This relies on massively-parallel sequencing of transposon-flanking regions and simultaneously assigned the insertion site and phenotype of over 90% of ST4/74 mutants screened in calves, providing data on the role of 2721 genes in intestinal colonisation (submitted). TraDIS has identified hundreds of novel virulence-associated loci (Fig. 3); however the data are specific to the role of genes in the distal ileal mucosa. MLNs serving the same region of the gut of the same animals used to screen the mutant library were collected and stored at -80°C. We have confirmed that these yield at least 10^7 colonies, enabling us to be ≥95% confident that absence of mutants from such pools will be due to their genotype rather than chance owing to sampling a population of an inadequate size. We will prepare genomic DNA from at least 10^8 colonies obtained from the 18 calves used to screen the mutant library. TraDIS will be

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- Avoid repetition of Track Record & Previous Research
- Focus on data in support of *this* application
- Needs to be convincing, not so preliminary as to seed doubt
- Demonstrate your skills &/or ability to probe an experimental system
- Make use of colour or graphics to sell your science

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Hypothesis & aims

Hypothesis

hʌɪˈpɒθɪsɪs/

noun

1. A supposition or proposed explanation made on the basis of limited evidence as a starting point for further investigation.

- The boundaries of hypothesis-driven & merely descriptive research are hard to define
- Not all proposals need a hypothesis (e.g. if developing a resource)
- If no hypothesis is stated it must be clear what gaps in knowledge you will address
- It may help to preface this section with the key questions in your area
- Should be clear, accessible & logically ordered

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Programme & Methodology

- Structure under the same objectives as listed elsewhere
- Around 3-5 Objectives is typical, avoid over-complicating with multiple tasks & sub-tasks
- Concisely & precisely describe how the research will be done, as if to a specialist in your field & the expert Introducing Member
- Assume a high level of technical knowledge, but ensure that any complex or unique aspects are adequately described
- Indicate the number of replicates & state justification for group sizes
- At the end of each objective it may help to specify timescale, milestones or deliverables (or indicate these in a Gantt chart)

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Risk & contingency plans

- Indicate how data & materials will be validated
- Ensure adequate controls are described
- Be honest about the risk of failure & indicate how risks are mitigated by experience, preliminary data or published work
- Articulate alternative plans for key experiments
- Avoid objectives that are strictly inter-dependent
- Show ambition, but not too much
- Propose work within the capability of yourself & the staff requested

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Concluding remarks

- A unifying closing paragraph or statement helps
- Aid the [weary] referees & IMs by reiterating the need for the proposed research & expected outputs
- Identify any particular strengths (foundation data, industry input, added-value to ongoing work)
- Consider directly addressing areas the referees will comment on (e.g. Timeliness & Promise, Impact & links to funder priorities)
- Avoid direct repetition of text elsewhere

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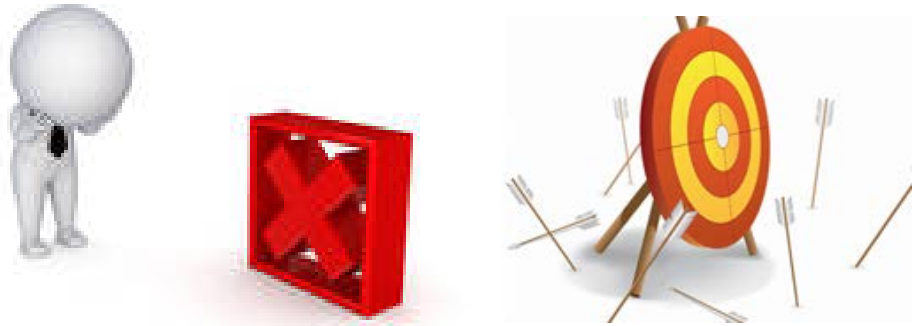
Common proposal faults



- Promises too much (over-ambitious)
- Promises too little (incremental extension of knowledge)
- Ignores funder priorities
- Lacks novelty or replicates work elsewhere
- Insufficient detail in experimental plan or ways to mitigate risk
- Inconsistencies between sections or illogical flow
- Poor standard of presentation
- Flaws in understanding
- Fails to get to the point or articulate a clear rationale or aim
- Lacks justification for the proposed approach or resources

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Before submission

- Consider the proposals Strengths, Weaknesses, Opportunities & Threats (SWOT analysis) & how to address them
- Ask colleagues to *critique* the proposal, not just read it
- Check format, spelling, grammar & referencing carefully
- Ensure all sections of the proposal are complete
- Where the text can be shortened without loss of clarity, do so
- Ensure all participants & institutions agree to the final version

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Looking ahead to the next session...

- Estimating costs
- Justification of resources
- Beneficiaries
- Impact Summary & Pathways to Impact
- Data management & sharing
- Approvals
- Response to referees
- Dealing with rejection
- Exercise

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