# 2017 Drug Discovery Initiative Registered Report
# INTRODUCTION AND GUIDELINES

Founded in 1978 as the National Neurofibromatosis Foundation, the Children's Tumor Foundation is a non-profit organization committed to identifying effective drug therapies for neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2) and schwannomatosis, and to improving the lives of those living with these disorders. NF is one of the most common of the rare diseases, affecting 1:3,000 individuals (around 100,000 persons in the US; and over 2 million worldwide). Since its inception, Children's Tumor Foundation has committed over $35 million to research grants and initiatives, supporting scientists around the world to conduct groundbreaking NF research.

NF causes a range of brain and nerve tumors (benign and malignant), bone abnormalities, learning disabilities, pain, vascular complications and other manifestations. The progress of NF is unpredictable and often presents a chronic lifelong burden to the affected person. There is a need for drug management but there is currently no effective therapy. The signaling pathways affected in NF are common to many other tumor disorders and many existing drugs developed for these disorders could be effective in NF.

The Drug Discovery Initiative (DDI) Awards supports early stage testing of candidate drug therapies for the treatment of neurofibromatosis (NF): NF1, NF2, and Schwannomatosis. This award mechanism has been a catalyst program that has helped to fuel the drug pipeline with promising leads. DDI awards have yielded over $5M dollars in follow on funding from the federal government and other sources as well as multiple industry collaborations and publication. To keep this momentum, the Children's Tumor Foundation has partnered with the scientific publisher PLOS to bring you the new 2017 Drug Discovery Initiative Registered Reports (DDI-RR), where particular emphasis on transparency in the research and peer review process has been placed.

Registered Reports emphasize the importance of the research question, and the quality of methodology by conducting peer review *prior to data collection*. Benefits of this collaboration include:

- Elimination of research bias in order to strive for publishable results
- Enhancing the transparency and reproducibility of science
- Ensuring that the specific work supported by the funder (the Children's Tumor Foundation) is undertaken
- Author stands to benefit by having their publications accepted in a respected journal before they start their research

**(DDI-RR)** Applicants submit high-quality protocols through ctf.org, and if approved, receive a DDI-RR funded grant by CTF as well as in principle acceptance (before data collection commences) for publication in *PLOS ONE*. This format is designed to minimize publication bias and several forms of research bias, while also allowing complete flexibility to conduct exploratory (unregistered) analyses and report serendipitous findings. Registered Reports represents a major departure from the standard research and peer review process, and is set to revamp the publishing landscape.

## Applicant Eligibility:

- Applicant should have an MD, PhD or equivalent and have full access to, or identified collaborators with, all required resources including all in vivo and in vitro models
- There is no citizenship requirement. Applications are welcomed from all qualified individuals worldwide
- As the program offers only seed funding, it is anticipated applicants already have established, in their laboratory, or have direct access to, any additional resources needed to complete the proposed research
- Applications are welcomed from both the academic and private sectors

**SPECIAL NOTE FOR FEDERAL EMPLOYEES (e.g. NIH intramural researchers)**

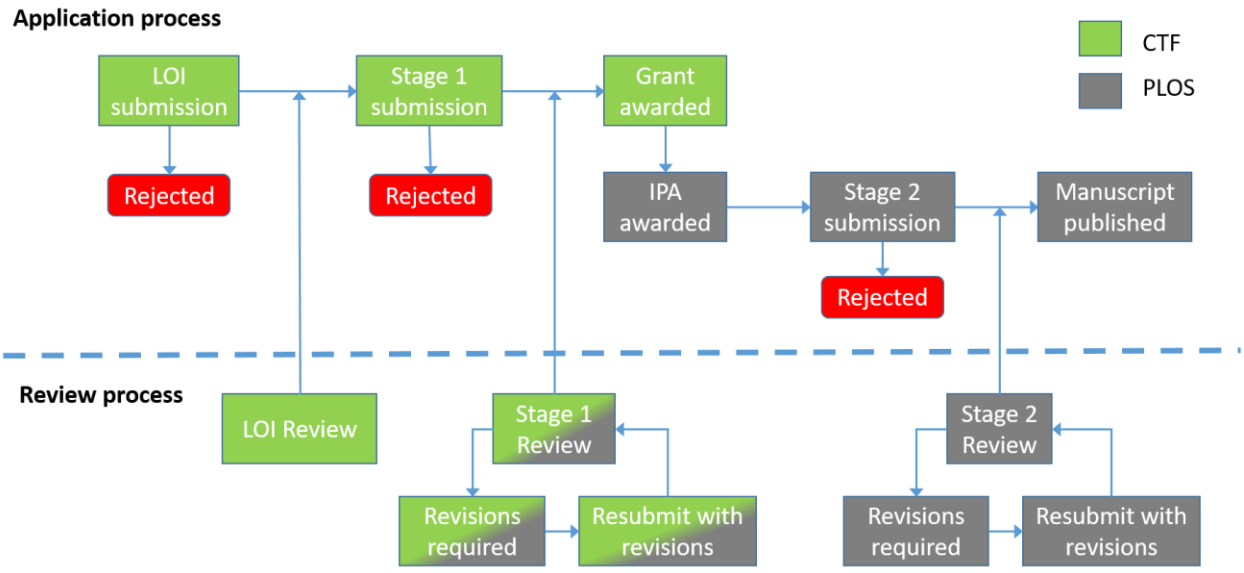
**For all of our funding awards, the Children's Tumor Foundation requires the CTF Patent Policy (in the attachment section) to be signed by all awardees and recipient institutions. The Children's Tumor Foundation has been advised that the National Institutes of Health are prohibited by congressionally enacted federal law from accepting the terms of the CTF Patent Policy. As a result, depending on the project being funded, the patent policy may be waived for federal employees (such as NIH intramural researchers). Federal employees wishing to apply for a grant are thus invited to inquire with CTF prior to submitting their grant proposal to discuss their project. Any information given will be treated confidentially.**

# APPLICATION PREPARATION AND GUIDELINES

Applicants submit a letter of intent (LOI), and if approved following this Triage Stage, are invited into Stage 1. The application will then be either rejected, asked to revise and resubmit, or approved for funding and given an In Principle Acceptance (IPA) for publication in *PLOS ONE*. The authors will then proceed to conduct the study within the agreed timeframe. Upon completion of the experiments, the grant will be considered completed and the applicant will be invited to include results in their finalized manuscript for re-review (Stage 2). In accordance with the PLOS data availability policy, applicants will upload the data to support the conclusions to a publicly accessible file-sharing service.

Stage 2 submission will be a *PLOS ONE*-only process where applicants must comply with *PLOS ONE* submission guidelines. The manuscript will be published regardless of the results. Please visit http://journals.plos.org/plosone/s/submission-guidelines for information on style, format, and manuscript organization for Stage 2 submissions.

**Workflow**




Applications received after the deadline will NOT be reviewed. The Foundation will not check or correct formatting errors. Applicants should retain electronic copies of submitted materials.

The program in 2017 is as follows:

- Up to $40,000* DDI in vitro Awards: to fund cell-based preclinical drug testing studies
- Up to $85,000* DDI in vivo Awards: to fund animal-based preclinical drug testing studies

***Total includes 10% indirect costs.**

Indirect costs MUST NOT exceed 10% of the total award. Indirect costs are those overhead administrative and facility costs which are not readily identifiable with the project but are nevertheless necessary for general operation. Examples of indirect costs include the salary and related benefits of individuals of administrative personnel, office supplies, rent, depreciation and utilities.

Applicants must provide the following documents (where applicable) during the online submission:

## Letter of Intent (LOI) Stage

Applicants will be asked to submit:

Letter of Intent

- The Letter of Intent should be two pages total, with an outline of the proposed research, including a description of the proposed experiments with rationale and preliminary data. It should also include a brief description of significance of the proposed experiments, timelines, and milestones of the research plan, as well as a summary of all resources available.

Biographical Sketch

- Detailing Education/training, positions of honors (if applicable), and selected peer-reviewed publications.

Budget Justification

- Please visit http://www.ctf.org/ddirrbudget for formatting and required information.

## Stage 1 Submissions should include a cover letter and manuscript

The cover letter should include:

- A statement confirming that all necessary support is in place and that approvals (e.g. ethics) are either already in place or how they will be obtained for the proposed research (e.g. to which approval body the protocol will be submitted to).
- An anticipated timeline for completing the study if the initial submission is accepted.
- A statement confirming that the authors agree to share the data to support the conclusions, in accordance with the PLOS data availability policy. Publication will be contingent on compliance with all *PLOS ONE* policies **(see for example http://journals.plos.org/plosone/s/submission-guidelines)**.
- A statement confirming that if the authors later withdraw their paper, they agree to the journal publishing a short summary of the pre-registered study as a Withdrawn Registration.

The manuscript should include the following sections:

Introduction

- A review of the relevant literature that motivates the research question and a full description of the experimental aims and hypotheses. Please note that following IPA, the Introduction section cannot be altered (see below).

Methods

- Full description of proposed sample characteristics, including criteria for data inclusion and exclusion (e.g. outlier extraction). Procedures for objectively defining exclusion criteria due to technical errors or for any other reasons must be specified, including details of how and under what conditions data would be replaced.

- A description of experimental procedures in sufficient detail to allow another researcher to repeat the methodology exactly, without requiring further information (please include details of key reagents e.g. animal models, cell lines, antibodies, small molecules etc.). These procedures must be adhered to exactly in the subsequent experiments or any Stage 2 manuscript can be rejected.

- Proposed analysis pipeline, including all preprocessing steps, and a precise description of all planned analyses, including appropriate correction for multiple comparisons. Any covariates or regressors must be stated. Where analysis decisions are contingent on the outcome of prior analyses, these contingencies must be specified and adhered to. Only pre-planned analyses can be reported in the main Results section of Stage 2 submissions. However, unplanned exploratory analyses will be admissible in a separate section of the Results (see below).

- For studies involving statistical analyses, justification for the method used must be provided along with all relevant details. For Neyman-Pearson inference please include a statistical power analysis and estimated effect size. For Bayesian hypothesis testing, please include predictions and corresponding Bayes factor, along with distributions and parameters to be used (if resources are limited, please specify the maximum feasible sample size at which data collection would have to cease). For more details regarding statistical methods, see below.

- Full descriptions must be provided of any outcome-neutral criteria that must be met for successful testing of the stated hypotheses. Such quality checks might include the absence of floor or ceiling effects in data distributions, positive controls, or other quality checks.

- Timeline for completion of the study and proposed resubmission date if Stage 1 review is successful. Extensions to this deadline can be negotiated with the editor.

- Any description of prospective methods or analysis plans should be written in future tense.

Pilot Data

- Optional. Can be included to establish proof of concept, effect size estimations, or feasibility of proposed methods. Any pilot experiments will be published with the final version of the manuscript and will be clearly distinguished from data obtained for the pre-registered experiment(s).

**Authors are reminded that any deviation from the stated experimental procedures, regardless of how minor it may seem to the authors, could lead to rejection of the manuscript at Stage 2.** In cases where the pre-registered protocol is altered after IPA due to unforeseen circumstances (e.g. change of equipment or unanticipated technical error), the authors must provide detailed explanations in the Stage 2 submission so that these can be evaluated by the editors.

Once the study is complete, authors prepare and resubmit their manuscript for full review, with the additions below. All manuscripts must conform to *PLOS ONE* submission guidelines and editorial policies (**see for example http://journals.plos.org/plosone/s/submission-guidelines)**.

## Stage 2 Submissions should include:

(Once research is concluded)

In accordance with the PLOS data availability policy, data underlying the findings must be made freely available in a public repository. Data files should be appropriately time stamped to show that data was collected *after* IPA and not before. Other than pre-registered and approved pilot data, no data acquired *prior* to the date of IPA is admissible in the Stage 2 submission. The data must be accompanied by guidance notes, where required, to assist other scientists in replicating the analysis pipeline. Authors are also encouraged to upload any relevant analysis scripts and other experimental materials that would assist in replication (e.g. stimuli & presentation code).

- We support other initiatives advancing the openness and transparency of published results:

  PLOS has partnered with protocols.io and researchers are encouraged to deposit their laboratory protocols, obtain a unique DOI and link to these from the Methods section of their articles. For computer code we support sharing via platforms such as CodeOcean; authors are encouraged to link to code depositions from within the submitted manuscript.

- Any supplementary figures, tables, or other text (such as supplementary methods) can either be included as standard supporting information that accompanies the paper, or they can be archived together with the data. Please note that the underlying data should be archived (see above) rather than submitted to the journal as supplementary material.

- The authors must collectively certify in the resubmission Cover Letter that all non-pilot data was collected after the date of IPA.

Background, Rationale and Methods

- Apart from minor stylistic revisions, such as changing the future tense to past tense for description of the plans, and important updates to background literature, **the Introduction cannot be altered from the approved Stage 1 submission, and the stated hypotheses cannot be amended or appended**. Any textual changes to the Introduction or Methods (e.g. correction of typographic errors, updates on background literature) must be clearly marked in the Stage 2 submission. Any relevant literature that appeared following the date of IPA should be covered in the Discussion.

Results & Discussion

- The outcome of all registered analyses must be reported in the manuscript, except in rare instances where a registered and approved analysis is subsequently shown to be logically flawed or unfounded. In such cases, the authors, reviewers, and editor must agree that a collective error of judgment was made and that the analysis is inappropriate. In such cases the analysis would still be mentioned in the Methods but omitted with justification from the Results.

- It is reasonable that authors may wish to include additional analyses that were not included in the registered submission. For instance, a new analytic approach might become available between IPA and Stage 2 review, or a particularly interesting and unexpected finding may emerge. Such analyses are admissible but must be clearly justified in the text, appropriately caveated, and reported in a separate section of the Results titled "*Exploratory analyses*". Authors should be careful not to base their conclusions entirely on the outcome of statistically significant *post hoc* analyses.

- Authors reporting null hypothesis significance tests will be required to report exact *p* values and effect sizes for all inferential analyses.

*Suggestions on statistical analysis*

- *We recommend that studies involving Neyman-Pearson inference include a statistical power analysis. Estimated effect sizes should be justified with reference to the existing literature. Since publication bias overinflates published estimates of effect size, power analysis should be based on the lowest available or meaningful estimate of the effect size. The a priori power should be 0.9 or higher for all proposed hypothesis tests. In the case of highly uncertain effect sizes, a variable sample size and interim data analysis will be permissible but with inspection points stated in advance, appropriate Type I error correction for 'peeking' employed, and a final stopping rule for data collection outlined.*

- *Methods involving Bayesian hypothesis testing are also encouraged. For studies involving analyses with Bayes factors, the predictions of the theory must be specified so that a Bayes*

*factor can be calculated. Authors should indicate what distribution will be used to represent the predictions of the theory and how its parameters will be specified. For example, will you use a uniform up to some specified maximum, or a normal/half-normal to represent a likely effect size, or a JZS/Cauchy with a specified scaling constant? For inference by Bayes factors, authors must be able to guarantee data collection until the Bayes factor is at least 10 times in favor of the experimental hypothesis over the null hypothesis (or vice versa). Authors with resource limitations are permitted to specify a maximum feasible sample size at which data collection must cease regardless of the Bayes factor, however to be eligible for in-principle acceptance this number must be sufficiently large that inconclusive results at this sample size would nevertheless be of major importance.*

# REVIEW GUIDELINES

## Review Process

**During the Triage Stage (Letter of Intent – LOI)**, applicants are reviewed by the Children's Tumor Foundation's DDI Chairs, and CTF's Internal Review Committee. Reviewers will consider:

1. Impact of the proposed research
2. Feasibility of proposed study
3. Alignment of budget
4. Applicant qualifications

Based on an assessment of these merits, the DDI-RR Review Committee will select and recommend applications for approval into stage 1.

**During Stage 1,** applications are reviewed by the Children's Tumor Foundation's Review Committee members and *PLOS ONE* Editors.

In considering applications at the Stage 1, reviewers will be asked to assess the proposal in greater detail with emphasis on:

1. The logic, rationale, and plausibility of the proposed hypotheses.
2. The soundness and feasibility of the methodology and analysis pipeline (including statistical power analysis where appropriate).
3. Whether the clarity and degree of methodological detail is sufficient to exactly replicate the proposed experimental procedures and analysis pipeline.
4. Whether the authors have pre-specified sufficient outcome-neutral tests for ensuring that the results obtained are able to test the stated hypotheses, including positive controls and quality checks.

Applicants' Proposals that satisfy these criteria will receive an award letter detailing the necessary reporting schedule, and will be issued an in principle acceptance (IPA) from *PLOS ONE*, indicating that the article will be published pending completion of the approved methods and analytic procedures, passing of all pre-specified quality checks, and a defensible interpretation of the results. Stage 1 protocols are not published following IPA. Instead they are held in reserve by the journal and integrated into the completed article following approval of the final Stage 2 manuscript. Authors have the option to also deposit their Stage 1 protocols on a registration platform such as the Open Science Framework registry (http://osf.io/registries/) as a public deposit.

**In considering papers at Stage 2**, applications are reviewed by *PLOS ONE* Editors only. Reviewers will be asked to decide:

1. Whether the data are able to test the authors' proposed hypotheses by satisfying the approved outcome-neutral conditions (such as quality checks, positive controls)
2. Whether the Introduction, rationale and stated hypotheses are the same as the approved Stage 1 submission
3. Whether the authors adhered precisely to the registered experimental procedures
4. Whether any unregistered *post hoc* analyses added by the authors are justified, methodologically sound, and informative
5. Whether the authors' conclusions are justified given the data

**Reviewers are informed that editorial decisions will not be based on the perceived importance, novelty or conclusiveness of the results.** Thus while reviewers are free to enter such comments on the record, they will not influence editorial decisions. Reviewers at Stage 2 may suggest that authors report additional post hoc tests on their data; however authors are not obliged to do so unless such tests are necessary to satisfy one or more of the Stage 2 review criteria.

## TERMS OF AWARD

Applicant Notification

Applicants will be notified as soon as possible as to the outcome of the review. The target timeframe being about 2 weeks after submission of the triage (LOI) stage, and 9-10 weeks from Stage 1 submission date to applicant notification. Stage 2 submissions will undergo peer review at the journal. Time frames vary typically from a few weeks to a few months. Based on the prior assessment at Stage 1, we expect a faster than average turnaround compared to regular submissions. All applicants, both funded and not funded, will be provided with a Statement Summary of feedback highlighting the key comments of the reviewers.

## Registered Report Activation and Payment

Payment will be activated as soon as the Awardee and Institution officials sign the following documents:

1. Acceptance of DDI-RR Award: Accepting the Children's Tumor Foundation Terms of Award (see below).
2. Patent Policy (see below)

## Manuscript withdrawal and *Withdrawn Registrations*

It is possible that authors with IPA may wish to withdraw their manuscripts following or during data collection. Possible reasons could include technical error, an inability to complete the study due to other unforeseen circumstances, or the desire to submit the results to a different journal. In all such cases, manuscripts can of course be withdrawn. However, the journal will publicly record each case as *Withdrawn Registrations*. This section will include the authors, proposed title, the abstract from the approved Stage 1 submission, and brief reason(s) for the failure to complete the study. Partial withdrawals are not possible; i.e. authors cannot publish part of a registered study by selectively withdrawing one of the planned experiments. Such cases must lead to withdrawal of the entire paper. Studies that are not completed by the agreed Stage 2 submission deadline (which can be extended in negotiation with the editorial office) will be considered withdrawn and will be subject to a Withdrawn Registration.

## Award Cancellation or Early Termination

In the event an award is cancelled or terminated, the award amount will be prorated on the basis of the number of months it was in effect. A final financial report of award expenditures and a refund of any monies unexpended during the period of the award must be submitted to Children's Tumor Foundation within 60 days after cancellation or termination. Note: Failure to provide Progress Reports and Expenditure Reports by the required dates will result in a suspension of the award until the materials are received.

## Patent Policy Relating to Foundation Funded Research

Prior to activation of Children's Tumor Foundation funding awards, the awardee's institution must sign the Children's Tumor Foundation Patent Policy. We strongly recommend agreeing and signing the Patent Policy at the time of application submission in order to speed up the process of award assignment. If your institution is not able to agree to the terms of the Patent Policy as they stand, please contact the foundation as soon as possible at grants@ctf.org. The Patent Policy is intended to ensure that any inventions or patented technologies arising from research supported by the Children's Tumor Foundation are commercialized where possible. Children's Tumor Foundation anticipates recouping some revenues arising from commercialized technologies it has supported, that is in proportion to the contribution made by the funding initially provided by the Children's Tumor Foundation.

## DDI – RR Reporting

Progress Reports must be submitted to the Foundation at 6 months and 12 months after the commencement of funding. A template for these reports and reminders to submit will be sent via email. When reporting, if acknowledging that content includes details of unpublished work, details will not be made public by the Foundation. However high-level outcomes from these reports (e.g. successful hit in vivo/in vitro; tumor type represented by assay; etc.) will be used in summary reports to the Foundation's Board of Directors, donors, etc.

## DDI – RR Financial Reporting

A financial statement must be provided to Children's Tumor Foundation itemizing expenditures for the Registered Report Award at the completion of funding. This report is due within 60 days after the end of the anticipated 12-month period during which the award will be used. Links to reporting templates will be sent via email. Financial reports should be signed both by the awardee and by the responsible institutional financial officer. Any unexpended and uncommitted funds in the possession of the awardee at the end of the award period shall be returned to the Foundation within 60 days of the end of the award. In addition to the above, interim accounting may be requested by the Children's Tumor Foundation.

## Status of Personnel Compensated Under DDI-RR

The awardee shall be considered an employee of the awardee's institution, and not of the Foundation.

## Extended leaves of absence

Should the awardee need to take a leave of absence for over a month (i.e. maternity/paternity leave, illness, etc.), the Foundation must be informed of the date of departure and expected date of return. *PLOS ONE* needs to be involved if the absence is expected to lead to delays to the paper submission.

## DDI-RR Status Change or Transfer of Institutions

Any fundamental change in the purpose for which DDI-RR was originally made must have prior written consent of the Foundation. Awards may not be transferred from one institution to another without prior written authorization from the Foundation. *PLOS ONE* needs to be informed if this leads to any changes to the experimental designs.

## Follow-on Funding

As a condition of this award, grantees are required to provide the Children's Tumor Foundation any information about the research funded in this award as it pertains to follow-on funding, collaborations, publications, etc. This information will be requested annually via our online system for a period of 5 years following the end of the award period. These continuing communications with grantees will allow us to more easily measure the impact of our research funding.

### Publications or Exhibits of an Awardee

The Foundation should be notified at the time of public disclosures by the awardee based on their work supported by a Foundation. This includes when a paper is published in a scientific or medical journal, or when a presentation (e.g. poster, slide presentation) is made before a professional scientific or medical organization. All such publications or presentations based on work supported by the Foundation must credit in acknowledgements support from Children's Tumor Foundation. The Foundation requests that the awardee submits to the Foundation an electronic (PDF or Word) copy of the paper, abstract with slide presentation, or copy of the poster materials. This material should be forwarded to the Foundation - if possible once accepted for publication or presentation, and certainly, immediately following publication or presentation, together with the name of the publication or the organization accepting it, and the time and place of the meeting. Information should be sent to grants@ctf.org. This information shall be considered confidential by the Foundation until publicly presented or published by the awardee. The Foundation will coordinate

with the awardee in promoting the presentation or publication on the Children's Tumor Foundation website (www.ctf.org) or in other Foundation communications to its constituents (E-News blast, NF Newsletter, website, etc.)