Expansion of the Test of Rapamycin in Aging Dogs (TRIAD) Clinical Trial

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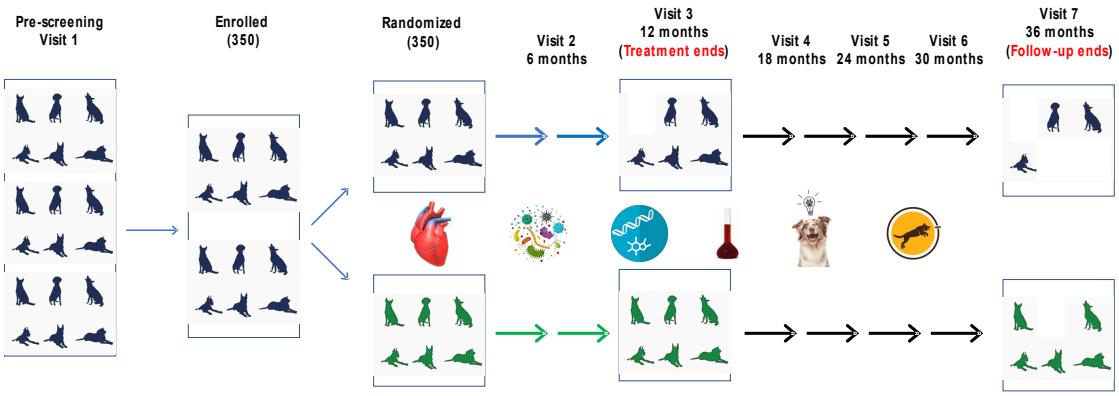
The goal of this proposal is to increase enrollment in the TRIAD clinical trial from 350 dogs to 580 dogs. The rationale is to provide sufficient sensitivity to detect a 9% increase in lifespan, thus greatly increasing the likelihood of a successful outcome for the trial. The requested funding level is **$2.5 million**.

The Test of Rapamycin in Aging Dogs (TRIAD) is a randomized, double-blind, placebo-controlled clinical trial testing whether the drug rapamycin can slow aging and increase lifespan in middle-aged companion dogs. TRIAD is being conducted as part of the Dog Aging Project (www.dogagingproject.org) at the University of Washington. Dogs must be at least 7 years old and between 40-100 lbs in weight at the time of enrollment. The study period is for 3 years from enrollment, consisting of one year of treatment followed by two years of observation. Lifespan is the primary endpoint for TRIAD. Secondary endpoints include age-related changes in cardiac function, activity, cognitive function, disease incidence, serum metabolome, fecal microbiome, and blood epigenome.



Schematic design of TRIAD. 350 healthy dogs at least 7 years of age and between 40-100 lbs in weight will be enrolled at one of the TRIAD clinical sites. Equal numbers will be randomized to placebo (blue) and treatment (green) groups. Dogs will be seen at baseline and every six months for three years, consisting of a one year treatment period and a two year follow-up observational period. At each visit dogs will undergo a standard exam, blood chemistry, urinalysis, cognitive assessment, and echocardiogram. Samples will be obtained for serum metabolome, fecal microbiome, and blood epigenome. Activity monitoring will occur periodically throughout.

TRIAD is funded through a grant from the National Institute on Aging (U19AG057377) which provides sufficient resources to enroll 350 dogs (175 placebo + 175 rapamycin) into the trial. This cohort size provides power of 0.8 to detect a 36% increase in life expectancy, which corresponds to a 14% increase in average lifespan for this cohort. Increasing the total enrollment to 580 dogs would provide power of 0.8 to detect a 24% increase in life expectancy, which corresponds to a 9% increase in average lifespan. The 9% threshold is important, because

two studies using similar designs to TRIAD reported median lifespan extension in mice of approximately 9%[1,2].

Logistics and Timeline: The infrastructure to support TRIAD (recruitment, retention, clinical sites, approvals, study drug and placebo, etc.) has been created over the past 2.5 years. The first TRIAD participants have completed the consent process and Initial appointments are being scheduled now at our veterinary teaching hospital clinical sites. We anticipate screening at least 100 dogs by the end of 2021 with the remaining dogs screened and enrolled in the first half of 2022. Expansion of the study to 580 dogs would likely extend the enrollment phase to the end of 2022. Initial analysis of secondary endpoints would be possible when the first dog completes the treatment phase (end of 2023) and the lifespan analysis and final secondary endpoint analysis would occur at the end of the observation phase (end of 2025).

Itemized Budget: This budget projection estimates the costs to expand TRIAD to 580 dogs over the entire study period (2022-2025). Personnel costs include an assistant study manager and partial support for TRIAD veterinary techs at each clinical site and record screening during enrollment. Fixed costs (per visit) include exam, echocardiograms/EKG, blood chemistry, urinalysis, inflammatory assays, metabolomics, microbiome, and epigenome. Miscellaneous costs include funds for supporting treatment in the case of adverse events and targeted recruitment near clinical sites and retention efforts as needed. The University of Washington adds a 5% fee to all donations over $10,000. There is no additional overhead for donations.

Budget Period: 2021-2025

Personnel:	$486,000
Drug costs:	$375,000
Clinical costs:	$1,308,700
Biobank and shipping:	$103,500
Miscellaneous:	$70,000
UW Fee (5%):	$117,160
Total:	**$2,460,360**

References:

1 Harrison, D. E. *et al.* Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* **460**, 392-395, doi:nature08221 [pii]
10.1038/nature08221 (2009).

2 Bitto, A. *et al.* Transient rapamycin treatment can increase lifespan and healthspan in middle-aged mice. *eLife* **5**, e16351, doi:10.7554/eLife.16351 (2016).