NON-TECHNICAL SUMMARY (NTS)

Project Title (max. 50 characters)	Molecular regulation of development	
Key Words (max. 5 words)	Development, zebrafish, embryo, mechanism	
Expected duration of the project (yrs)	5	
Purpose of the project as in ASPA section 5C(3) (Mark all boxes that apply)	X	Basic research
	X	Translational and applied research
		Regulatory use and routine production
		Protection of the natural environment in the interests of the health or welfare of humans or animals
		Preservation of species
		Higher education or training
		Forensic enquiries
	X	Maintenance of colonies of genetically altered animals[1]
Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)	This project aims to increase our understanding of development and diseases at the molecular level. Developmental defects and diseases are remarkably common in both humans and animals and they frequently cause lifelong ill-health and premature death. The vast majority have no known cause, due to the often complex nature of their aetiology and no approved treatments. There is a significant need to the underlying mechanisms of these complex diseases in order to find new avenues of treatment. We model the disease in zebrafish and investigate those animals to find out how molecular pathways are disrupted, how this leads to the disease pathology and identify which aspects of the disease we should be targeting with treatment.	
What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the project)?	We expect to increase our understanding of several diseases, predominantly neurodevelopmental diseases that affect children and are occurring at an increasingly high rate in the population. This may allow us to propose new treatment strategies for these diseases.	

[1] At least one additional purpose must be selected with this option.

What species and approximate numbers of animals do you expect to use over what period of time?	We use the zebrafish as our experimental model. The embryos develop externally from the mother and do not become free-feeding and regulated under ASPA until 5 days post-fertilisation. The majority of the diseases we model affect embryos at unregulated stages so most of our studies are not regulated. However, we do need to maintain and breed both normal and existing zebrafish mutant lines that model developmental diseases in order to study their embryos up to 5 days post fertilisation. These lines do come under regulation. At regulated ages, we expect to use 8000 genetically altered zebrafish over a 5 year period, of which all would be classified as non-harmful mutants. Any embryos produced by these zebrafish that are employed in experiments as opposed to breeding will only be used up to 5 days post fertilisation.
In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?	The non-harmful zebrafish mutants will be used for the production of embryos between the ages of 4 months-2 years (the period of most effective breeding). There are no harmful effects expected from this breeding strategy. Once the zebrafish have reached the end of their breeding life, they will be humanely euthanised.

Application of the 3Rs	
1. Replacement State why you need to use animals and why you cannot use non-animal alternatives	Vertebrate development requires the co-ordinated growth, differentiation and movement of diverse tissues in time and space. While it is possible to model simple aspects of development in vitro, it is impossible to model the complex events that occur between tissues to form a fully functional embryo. Furthermore, pathogenic processes during disease, and attempts to treat them, involve many cell types and tissues and this cannot be recreated in vitro. It is for these reasons we must undertake experiments upon animals. Our species of choice is the zebrafish which are unregulated up to 5 days post-fertilisation. Most of our experiments are performed on these unregulated animals.
2. Reduction Explain how you will assure the use of minimum numbers of animals	To ensure minimum numbers are used, we will perform pilot studies and use power calculations to determine the number of animals required and take those numbers into account when deciding on the most appropriate assays to use.
3. Refinement Explain the choice of species and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.	We use the zebrafish model as a substantive body of work shows that developmental processes are highly conserved between vertebrates and because it is the vertebrate model with the lowest neurophysiological sensitivity. Thus, data derived from our models can be extrapolated to humans and other animals. The protocols to be used are all standard methods in zebrafish research. Due to the wide variety of resources available, we will use existing non-harmful mutants in our research. With the exception of the minor surgery of regenerating fin tissues in order to genotype, all of the treatments are non-surgical. Latest knowledge on analgesia will be applied.