

Impact case study (REF3)

Institution: University of Stirling		
Unit of Assessment: 4. Psychology, Psychiatry and Neuroscience		
Title of case study: Improving the Health and Wellbeing of Laboratory-housed Animals		
Period when the underpinning research was undertaken: 2000-2017		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Hannah Buchanan-Smith Laura Scullion Hall (née Hall)	Professor Research Fellow	1995-Present 2011-2020
Period when the claimed impact occurred: 1 August 2013 to 31 December 2020		
Is this case study continued from a case study submitted in 2014? No		
<p>1. Summary of the impact</p> <p>Research at the University of Stirling has improved the health and wellbeing of many thousands of primates and dogs used in laboratory research and testing across the world. This is a result of our evidence-based Refinements to:</p> <ul style="list-style-type: none"> • positive reinforcement protocols and validation of welfare assessment indicators (Impact 1); • the procedure for oral compound delivery and housing for dogs (Impact 2); • cage sizes for all primates: 5-15 fold volume increase for marmosets & tamarins (Impact 3). <p>These Refinements have been incorporated into the animal welfare guidelines of the National Centre for the Reduction, Refinement and Replacement of Animals in Research (Impact 4), which underpin humane animal research.</p> <p>Overall impacts: this improved welfare for laboratory animals means they are more “fit for purpose” as models of human biological functioning, increasing the reliability and validity of scientific output and therefore also having substantial cost savings during drug development.</p>		
CONTEXT & RESEARCH	DIRECT WELFARE IMPACTS	OVERALL IMPACTS
<p>Poor animal welfare reduces findings' reliability and validity.</p> <p>We research training, oral gavage, and cage sizes to increase welfare.</p>	<p>1: Positive reinforcement protocols & validation of welfare indicators.</p> <p>2: Refined procedure for oral gavage.</p> <p>3: Larger primate cage sizes.</p> <p>4: Animal welfare guidelines enhanced.</p>	<p>Improved scientific outputs and economic benefits due to more reliable, valid results.</p>
<p>2. Underpinning research</p> <p>Improving the welfare of the 200,000+ dogs and primates used in laboratory research and testing globally is not only an ethical imperative given their capacity to suffer, but also increases the reliability and validity of the results of the studies conducted upon these animals (as stress affects biological functioning). Our research has validated interdisciplinary methods used for welfare assessment, as well as evaluating and providing evidence-based improvements to housing, husbandry and scientific procedures for primates and dogs in laboratories. This follows the 'Refinement' principle of the 3Rs framework for more humane animal research (see NC3Rs.org). Stirling research has been at the forefront, as improvements to the world-leading UK animal welfare standards ratchet those internationally.</p> <p>Bassett et al. (2003) (see output R1) demonstrated that positive reinforcement protocols can be used to train marmosets so they can be weighed in their home cages and provide urine samples on request. This avoids stressful capture and handling, and negates the need for stressful single housing in a metabolism cage. Findings showed trained marmosets had a reduction in the “stress hormone” cortisol, which was validated against behaviours indicative of better welfare compared to controls, meaning trained monkeys had better biological functioning and were more “fit for purpose” as healthy models. We also evidenced an infant rearing practice for large litters of marmosets that does not adversely impact their welfare (R2). We developed research-based training protocols for macaques and dogs (R3) that improve welfare. This research has underpinned Impacts 1 and 4, detailed below.</p>		

Oral gavage is a technique frequently used to deliver a compound via a tube directly into the stomach. Gavage is aversive and the frequency of its use is a cause for welfare concern. Using our Welfare Assessment Framework, incorporating behaviour, cardiovascular and affective measures, Hall et al. (2015) (**R3**) showed that sham dosing (an attempt to habituate dogs to dosing) is ineffective and 'primes' rather than desensitises dogs to dosing. Our refined procedure delivers considerable benefits for welfare and quality of data. Research on pen design (**R4**) indicates other factors to consider to promote better welfare and better scientific endpoints for dogs. This research has underpinned **Impacts 2** and **4**, detailed below.

Adequate space reduces the incidence and frequency of abnormal behaviours (e.g. locomotor stereotypy), increases the diversity and complexity of natural behaviours, and is thus essential for good welfare and quality of scientific output. The vast majority of policy guidelines and legislation on research animals specified minimum cage sizes for laboratory-housed primates solely in terms of "unit body weight". Prescott and Buchanan-Smith (**R5**) argued that optimum cage size depends on body size, arboreality and cage use, home range size, mean daily path length and stereotypic behaviour, breeding success in captivity, and species predisposition, not body weight alone. We recommended that minimum cages sizes should be increased for all primates: and that greater space is even more important for tamarin welfare than for marmoset. Evidence substantiating the differences between tamarins and marmosets comes from both Buchanan-Smith's captive and field studies (**R6**) which relate natural history to the housing and captive care of tamarins. This research has underpinned **Impact 3** and **4**, detailed below.

3. References to the research

In all research cited below Buchanan-Smith was Principal Investigator, obtaining substantial funding (>GBP1,000,000 in 10 grants from BBSRC, UFAW & NC3Rs, including investment from industry: AstraZeneca, Charles River Laboratories, Covance, Harlan & GlaxoSmithKline). All references are peer-reviewed, and all except R5 resulted from peer-reviewed funded research. Current and former University of Stirling authors in **bold** text.

- R1. Bassett, Buchanan-Smith** et al. 2003 Effects of training on stress-related behavior of the common marmoset in relation to coping with routine husbandry procedures *J. of Appl. Anim. Welf. Sci.* 6, 221-233. doi.org/10.1207/S15327604JAWS0603_07 Bassett was Buchanan-Smith's BBSRC-funded PhD student.
- R2. Ash & Buchanan-Smith** 2016 The long-term impact of infant rearing background on the affective state of adult common marmosets (*Callithrix jacchus*). *App. Anim. Behav. Sci.* 174, 128-136. doi.org/10.1016/j.applanim.2015.10.009 Ash was Buchanan-Smith's NC3Rs-funded PhD student.
- R3. Hall, Robinson & Buchanan-Smith** 2015 Refining dosing by oral gavage in the dog: A protocol to harmonise welfare. *J. Pharm. & Toxicol. Methods*, 72, 35-46. doi.org/10.1016/j.vascn.2014.12.007 Prize winning paper (**NC3Rs, 2015**). Hall was Buchanan-Smith's BBSRC CASE PhD student; Robinson a collaborator from AstraZeneca.
- R4. Hall, Robinson, Finch & Buchanan-Smith** 2017 The influence of facility and home pen design on the welfare of the laboratory-housed dog. *J. Pharm. & Toxicol. Methods*, 83, 21-29. doi.org/10.1016/j.vascn.2016.09.005 Hall was post-doc on NC3Rs grant; Robinson (AstraZeneca) and Finch (Charles River Laboratories) are coauthors from industry.
- R5. Prescott & Buchanan-Smith** 2004 Cage sizes for tamarins in the laboratory. *Animal Welfare*, 13, 151-157. Coauthor Prescott was a BBSRC PhD student of Buchanan-Smith.
- R6. Buchanan-Smith, Hardie, Caceres & Prescott** 2000 Distribution and forest utilisation of *Saguinus* and other primates of the Pando Department, Northern Bolivia. *Int. J. of Primatol.* 21, 353-379. doi.org/10.1023/A:1005483601403 Coauthors Hardie & Prescott were BBSRC-funded PhD students, and Caceres an international collaborator.

4. Details of the impact

Worldwide, more than 200,000 primates and dogs are used in laboratory research (see stir.ac.uk/4bu & stir.ac.uk/4bx). Improving the welfare of these animals is an ethical imperative, and of public interest. The welfare of primates and dogs can be compromised when they live in restricted laboratory conditions and are exposed to the exacting requirements of research (e.g.

restraint, dosing), adversely affecting scientific output quality. Industry concerns therefore centre on welfare, public perception, good scientific output, and cost. Our research recommendations have directly caused the Refinement of care and scientific procedures for primates and dogs across the world by large pharmaceutical companies and Contract Research Organisations, contributing to major improvements in the welfare of many thousands of animals.

Impact 1: Positive Reinforcement Protocols & Validation of Welfare Indicators

It is now commonplace for facilities to use the guidance on housing, husbandry, and positive reinforcement training of primates developed from our research (**R1**, **R2**, **R5**). This is demonstrably evident at major research centres such as: the Central Institute for Experimental Animals (Japan, **SC1c**), who have also integrated our guidance into their own 2018 *Marmoset Lab Manual*; the University of Cambridge (>200 marmosets, **SC1f**); the Primate Research Institute (Kyoto University, Japan, **SC1g**); The Wisconsin National Primate Centre, USA, with ~ 1,600 primates (**SC1h**) and the Biomedical Primate Research Centre (BPRC; one of Europe's largest research primate centres with >1,200 primates) who indicate, “*Staff working at the BPRC have implemented the research recommendations from Buchanan-Smith's team on positive reinforcement training for macaques and marmosets, and ways to improve housing, rearing and to refine scientific procedures*” (Designated Veterinarian, BPRC, **SC1b**).

Our team developed an essential resource for marmoset welfare, Marmosetcare.com (**SC5a**, see Fig. 1). This is a good-practice guide providing videos of our validated welfare measures, and positive reinforcement training protocols. Marmosetcare.com has had >286,000 unique visitors from 200 countries, >50% from USA (since 1/8/2012) indicating global reach and uptake of our housing, husbandry, and training protocols (in UK, Europe, Japan and USA - **SC1b,c,f,g,h**).

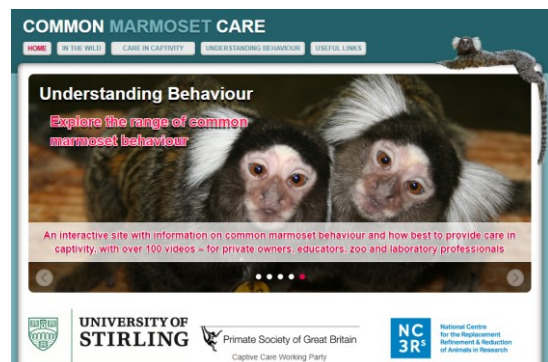


Figure 1 Stirling's marmoset website

Pathways to impact: In association with the Institute of Animal Technology, Continuing Professional Development (CPD) courses on “Training Primates Using Positive Reinforcement” (2005-2009) and on “Marmoset Behaviour and Welfare” (2004-2009) were run each year by Buchanan-Smith in Stirling (~25 participants/year). Such learning opportunities were enhanced with our open-access website Marmosetcare.com, developed by PhD student Watson and Buchanan-Smith, based on their research (**R1**, **R2**, **R5**). Our training recommendations (**R1**) were cited in the, still current, 2007 [International Primatological Society Guidelines](http://InternationalPrimatologicalSocietyGuidelines).

Impact 2: Refined Procedure for Oral Gavage and Housing of the Dog

Since April 2015, all UK grant applicants applying to perform oral gavage in dogs have had to use our refined methods (**R3**) of oral gavage to improve dog welfare, as applications are reviewed by the NC3Rs, or justify why not (see **Impact 4**). Since 2014, at Charles River Laboratories, Edinburgh, our research (**R4**) and our website RefiningDogCare.com (**SC5b**) “...led us to improve our training methods for research animals to cooperate with scientific procedures, and to refine oral gavage in the dog, concomitantly improving animal welfare. The publication on how dog welfare is influenced by housing is being incorporated into our new dog facility design” (Senior Director of Toxicology, **SC1d**). Similarly, since 2014 GlaxoSmithKline has transformed their dog training methods based on our research, increasing welfare and their research reliability, and has shared this best practice across its laboratories globally (**SC1a**).

Pathways to impact: The open access website RefiningDogCare.com was launched in 2016 by Scullion Hall and Buchanan-Smith (since 14/06/2016 it has had >20,000 unique visitors from >100 countries). Impact workshops with stakeholders were held (2014, 2015, 2017, including industry and Home Office representation) and accredited CPD training delivered onsite by Scullion Hall to all UK major dog users (2015-18).

Impact 3: Increased minimum cage sizes for primates

Throughout the impact window (Aug 2013 - Dec 2020) across Europe, minimum cage sizes have increased for primates in laboratories because of our research. In particular, marmosets and tamarins are now treated better (R5, R6). These genera have had significant increases in minimum floor area (from 0.25m²-0.5m² for marmosets and from 0.25m²-1.5m² for tamarins, see Fig. 2), and the minimum cage height for these genera is now 1.5m (over twice the previous 0.6m requirement). 100% of marmosets and tamarins (>8,000 animals NC3Rs figure, SC1e) in laboratories in the EU now benefit from larger cages and associated better welfare. As BPRC state, “these larger cage sizes, allow more natural social groupings, and greater opportunities to enrich the primates and lead directly to improved wellbeing (less negative behavior, more positive welfare indicators, including improved physical health)” (Designated Veterinarian, SC1b).

Pathways to impact: Our research (R5, R6) led directly to European [Directive 2010/63/EU](#) (in effect from 01/01/2013), which legislates for increased minimum cage sizes for marmosets and tamarins. This has been transposed into law in all EU states and reporting and inspections are required ([stir.ac.uk/4c9](#)). E.g. the 2014 UK Code of Practice (SC3) incorporated these changes and cites our research. The 2003 [non-human primates](#) report upon which the EU directive is based states: “It is more important to provide tamarins with a good volume of space than it is marmosets, if their wellbeing and breeding success are to be maximised (Prescott & Buchanan-Smith, in press [R5])” (SC2). The legislation refers only to Prescott and Buchanan-Smith’s work as the scientific basis for change in enclosure size. The volume increase

is 5 fold for two marmosets, and 15 fold for two tamarins (see Fig. 2). As the NC3Rs state, our “research on cage size had a direct impact on increasing the mandatory minimum space allocations for NHPs in [Annex III to Directive 2010/63/EU](#) (by 30% to 1400% depending on species, age/weight and grouping), through my [Prescott] memberships of the Primate Expert Group for Council of Europe Convention ETS 123 and Technical Expert Working Group for the Directive, thus benefiting around 8,000 NHPs per year used in the European Union since 2013. The positive welfare impact of this research by Buchanan-Smith and colleagues is thus far-reaching” (Director of Policy & Outreach, NC3Rs, SC1e).

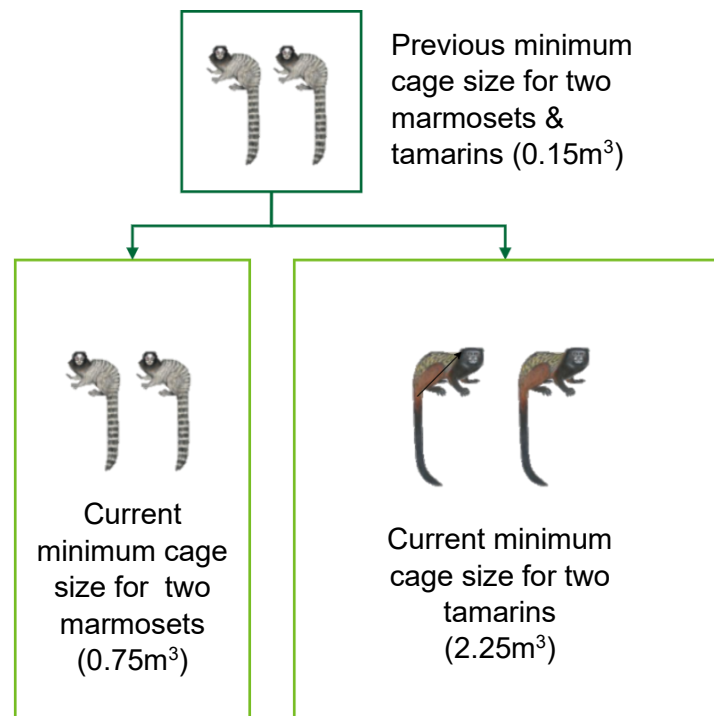


Figure 1. Illustration of increases in cage size (to scale)

Impact 4: Changes to animal welfare guidelines

The NC3Rs guidelines and website have incorporated our research recommendations. The NC3Rs is an organisation with teeth – it provides a service to review all UK proposals involving primates and dogs and advises on opportunities to implement the 3Rs, identify and address animal welfare concerns. This improvement in welfare standards has global reach, as, welfare standards must be consistent with principles of UK legislation for international collaborations. “The practical welfare implications of Buchanan-Smith and Scullion Hall’s research on improving laboratory dog welfare are included in the [NC3Rs web page on dog housing and care](#) [SC4]. This page has been viewed over 8,100 times by users in 95 countries ... Buchanan-Smith and Ash’s research on positive reinforcement training of non-human primates [R1], and on rearing of large litters of common marmosets without compromising welfare [R2], is incorporated into the 2017 version of the [NC3Rs Guidelines ‘Non-human Primate Accommodation, Care and](#)

*Use'. Implementation of the principles in the Guidelines is a condition of receiving funds from 15 organisations which support non-human primate (NHP) research internationally. Compliance is assessed by NC3Rs staff during peer review and laboratory visits (over 100 proposals reviewed and 25 awarded since October 2017)" (Director of Policy & Outreach, NC3Rs, **SC1e**).*

Overall Impacts

While commercial sensitivities and the nature of the impacts mean that the exact overall **economic benefits** of the Refinements detailed above are impossible to quantify, GlaxoSmithKline – the sixth largest pharmaceutical company in the world – considers our work with them on improving dog welfare to have brought it “financial benefits” (**SC1a**), a view also held by the BPRC (**SC1b**). Substantial reductions in testing costs occur because the outcomes of tests are more reliable and valid, and there is a reduction in unwanted variability, reducing numbers required to reach statistical significance. These economic benefits are likely to be high across the average 12.5 years and ~USD12,000,000,000 it takes to bring a new drug to market (stir.ac.uk/4cl). Costs can therefore be substantially reduced with better animal welfare, and reducing attrition, even modestly, can have huge financial savings and increased business growth (independently assessed by Graham and Prescott, 2015: [10.1016/j.ejphar.2015.03.040](https://doi.org/10.1016/j.ejphar.2015.03.040)).

In commercial pharmaceutical settings (i.e. outside of academia) our animal welfare impacts collectively contribute to “better scientific output as animal welfare and quality of scientific output are so closely linked” (BPRC, **SC1b**), a view also supported by testimony from GlaxoSmithKline and Charles River Laboratories (a multinational pharmaceutical company operating in 20 countries and who have contributed to 85% of United States Food and Drug Administration-approved drugs in use), who cite increased scientific output reliability (**SC1d**) due to our research-informed Refinements.

5. Sources to corroborate the impact

SC1. Testimonials from Research Users:

- **SC1a.** Veterinary Surgeon, GlaxoSmithKline, Hertfordshire, UK.
- **SC1b.** Designated Veterinarian, Biomedical Primate Research Centre (BPRC), The Netherlands.
- **SC1c.** Department Head, Department of Marmoset Biology and Medicine, Central Institute for Experimental Animals, Japan.
- **SC1d.** Senior Director of Toxicology, Charles River Laboratories, Edinburgh, UK.
- **SC1e.** Director of Policy and Outreach, NC3Rs.
- **SC1f.** Named Veterinary Surgeon, University of Cambridge, UK.
- **SC1g.** Veterinarian Primate Research Institute, Kyoto University, Japan.
- **SC1h.** Wisconsin National Primate Research Center, USA.

SC2. Council of Europe, Working party for the preparation of the fourth multilateral consultation of parties to the European convention for the protection of vertebrate animals used for experimental & other scientific purposes (ETS 123), 6th Meeting, Strasbourg, 25-27 March 2003, “Species-specific provisions for Non-Human Primates Background information for the proposals presented by the Group of Experts on Non-Human Primates”: stir.ac.uk/4cc. See pp.15-18, Section 4.3 on enclosures – dimensions and flooring that link directly to Buchanan-Smith’s research.

SC3. Code of Practice for the Housing and Care of Animals Bred, Supplied or Used for Scientific Purposes, December 2014 (Home Office): stir.ac.uk/4cf. Increased cage sizes described on p.30, and Buchanan-Smith referenced on p.186, 192.

SC4. NC3Rs (2017) Guidelines on Primate Accommodation, Care & Use: stir.ac.uk/4ci. Contains direct reference to research outputs (i.e. Section 1.5 on socialisation and training (R1), 1.3.4 rearing in marmosets (R2), 4.1 on accommodation (R5), 4.3.1 cites SC5a).

SC5. University of Stirling Marmoset and Dog care websites:

- **SC5a.** The common marmoset care website coauthored by PhD student Watson & Buchanan-Smith. <http://www.marmosetcare.com/>
- **SC5b.** The Refining Dog Care website, coauthored by Scullion Hall & Buchanan-Smith providing resources for those working with dogs in research. <http://www.refiningdogcare.com/>