Assessing the use of telemetric devices in preclinical safety studies in non-human primates - data aggregation step

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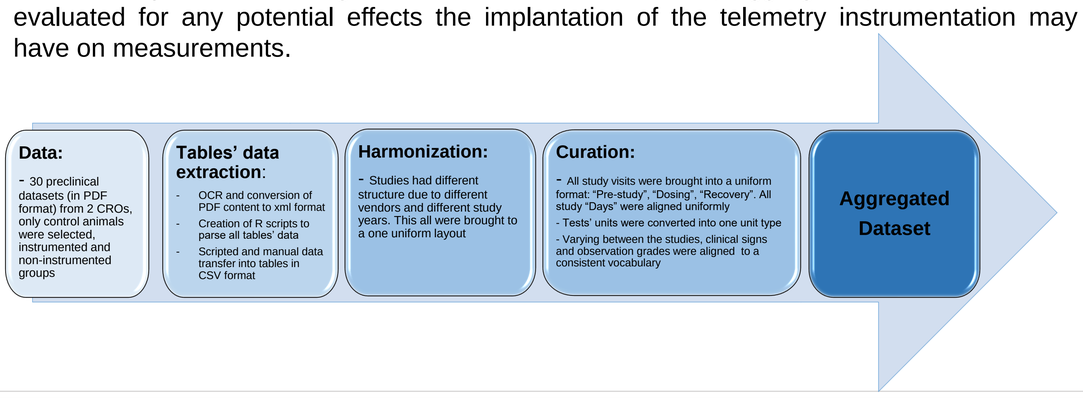
Background

Conventional monitoring of clinical and physiological measurements during experimentation can be intrusive, adding disruptive variables to study endpoints. In addition, there are growing societal concerns regarding the welfare, ethics and value of using large numbers of animals for medical research. The latter has encouraged focused development and application of the principles of replacement, reduction and refinement (3R's) in the use of animals in medical research.

Here, we evaluated if implanted telemetry instrumentation acquired data parallel conventional methods for quantifying physiological measurements. In addition, we compared clinical and pathology data for telemetry instrumented vs non-instrumented animals to assess for potential off target effects. Data was collected, aggregated, harmonized and evaluated for any potential effects the implantation of the telemetry instrumentation may have on measurements.



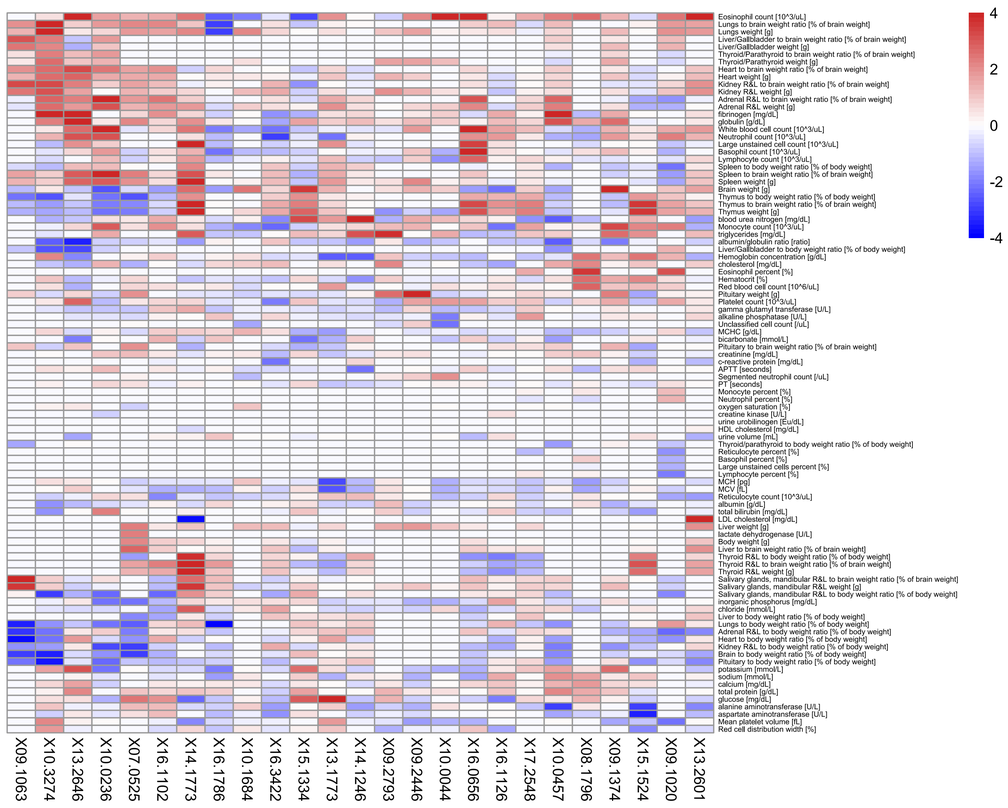
Data aggregation objectives

Thirty integrated general toxicology plus cardiovascular safety pharmacology preclinical studies carried out in Cynomolgus monkeys were selected for the aggregated datasets. The studies were standardized into a uniform format where test parameters, assessments and evaluations have the same structure, layout, parameter gradation system, and units.

The consolidated dataset can now be used for statistical analysis and help researchers answer many questions, for example:

1) Does surgical telemetry instrumentation impact clinical or physiological measurements over time as compared with non-telemetric (restrained and/or sedated, external leads) measurements?
2) In animals for which physiological data were recorded using both telemetric and non-telemetric methods, were the measurements comparable?
3) Does surgical telemetry instrumentation impact clinical or physiological measurements over time as compared with non-instrumented?
4) Are there any unforeseen adverse effects related to inclusion of surgically instrumented animals in a general toxicology study (i.e., ability to interpret, or negative impact on general toxicology outcomes, or safety pharmacology outcomes)?

Exploratory analysis of aggregated dataset



Heat map plot of mean difference of instrumented minus non-instrumented / SD (non-instrumented) for male (above) and female (below) animals

We conducted a brief exploratory analysis of several clinical, biochemical and physiological parameters to estimate an effect of animal instrumentation. All selected parameters were measured by conventional methods for instrumented and non-instrumented animals. Females (n=167) and males (n=176) were analyzed separately. Mean values for each of 174 parameters for each of 30 studies were calculated for instrumented and non-instrumented groups. To evaluate between-studies variation, the standard deviation for each parameter was calculated. The difference between parameters of instrumented and non-instrumented animals were divided by the standard deviation to give magnitude of effect.

Several clusters of parameters affected by instrumentation were identified (see heatmaps). Clustering may reflect the effect of study vendors, or other unaccounted factors. Several parameters had statistically significant ($p<0.05$) increase or decrease.

Parameter type	N parameters
absolute organ weight	35
clinical chemistry	37
coagulation	3
hematology	28
organ to body weight ratio	34
organ to brain ratio	34
pulse oximetry	1
urinalysis	2

Table 1. Parameters with the most significant unidirectional change across studies (males).

Parameter	N studies	direction	N studies with significant change	<0 (significantly)	>0 (significantly)	p value	mean difference (instrumented - non-instrumented)	mean non-instrumented	SD (non-instrumented)	mean difference/SD (non-instrumented)
globulin [g/dL]	24	increase	15	1	15	0.0001	0.35	3.06	0.48	0.73
albumin/globulin ratio [ratio]	24	decrease	14	14	1	0.0002	-0.17	1.44	0.26	-0.63
Eosinophil count [10^3/uL]	25	increase	15	3	15	0.0012	0.09	0.14	0.13	0.67
aspartate aminotransferase [U/L]	24	decrease	10	10	0	0.0014	-9.41	50.44	35.30	-0.27
MCH [pg]	25	decrease	11	11	1	0.0029	-0.55	23.44	1.44	-0.38
albumin [g/dL]	24	decrease	12	12	2	0.0043	-0.10	4.28	0.45	-0.21
total protein [g/dL]	24	increase	11	2	11	0.0094	0.26	7.35	0.64	0.40
gamma glutamyl transferase [U/L]	23	decrease	11	11	3	0.0249	-4.97	84.13	36.27	-0.14
alanine aminotransferase [U/L]	24	decrease	11	11	3	0.0262	-6.27	48.58	24.41	-0.26
MCV [fL]	25	decrease	**10**	10	3	0.0531	-1.35	75.70	4.50	-0.30

Table 2. Parameters with the most significant unidirectional change across studies (females).

Parameter	N studies	direction	N studies with significant change	<0 (significantly)	>0 (significantly)	p value	mean difference (instrumented - non-instrumented)	mean non-instrumented	SD (non-instrumented)	mean difference/SD (non-instrumented)
MCHC [g/dL]	24	decrease	13	13	1	0.0005	-0.47	30.82	1.45	-0.33
alanine aminotransferase [U/L]	23	decrease	10	10	0	0.0013	-9.21	53.19	29.62	-0.31
aspartate aminotransferase [U/L]	23	decrease	10	10	0	0.0013	-12.39	49.34	46.64	-0.27
globulin [g/dL]	23	increase	9	0	9	0.0029	0.35	3.13	0.45	0.77
albumin/globulin ratio [ratio]	23	decrease	12	12	2	0.0039	-0.18	1.36	0.27	-0.67
albumin [g/dL]	23	decrease	11	11	2	0.0088	-0.20	4.14	0.48	-0.42
Neutrophil count [10^3/uL]	19	increase	7	0	7	0.012	0.92	5.74	2.75	0.33
alkaline phosphatase [U/L]	23	decrease	13	13	5	0.0345	-47.21	325.24	133.07	-0.35
Lymphocyte count [10^3/uL]	24	decrease	10	10	3	0.0513	-0.61	6.26	2.40	-0.25
MCH [pg]	24	decrease	11	11	4	0.0617	-0.54	23.39	1.73	-0.31

Our brief analysis indicates that the surgical telemetry instrumented cohort has several parameters that differ significantly from the non-instrumented cohort. However, only 5% of the analyzed parameters are different between cohorts, and most of these are related to hematology and clinical chemistry. There are additional factors that should be considered in future data exploration: the direction of parameters change – decrease or increase, how parameters correspond to normal ranges, is sample size sufficient for statistical inference, etc.

The consolidated dataset provides unique opportunity to investigate the effect of instrumentation on laboratory animals and can answer the question how to accurately compare telemetrically obtained data with the data collected by traditional methods.