Supplemental Material for: Quality Assurance of Quantitative Cardiac T1-mapping in Multicenter Clinical Trials – A T1 Phantom Program from the Hypertrophic Cardiomyopathy Registry (HCMR) Study

This material supplements the technical details of the phantom quality assurance (QA) program development. We provided the phantom manufacture details in Section S1, QA protocol specification in Section S2 and ShMOLLI QA equation in Section S3. We described an additional experiment on T1 underestimation and inadequate Mz relaxation in Section S4. We attached supplemental data of T2 characteristics in **Figure S4, Figure S5**, full data samples for establishing QA model in **Figure S6** and **Figure S7**, and a complete list of sites providing the phantom scans for this study in **Table S1**.

Section S1: HCMR phantom manufacture

A batch of 50 multi-compartmental phantoms was manufactured in October 2013. Each phantom has nine compartments, encased in widely available universal clinical sample containers (Sterlin 128A, sigma.aldrich.com, **Figure S1a**) filled with water-based (18MΩ deionized H_2O, NANO pure Water Purification Systems, Model D11931, Thermo Scientific Barnstead, www.thermofisher.com) gels using agar and carrageenan, doped with $NiCl_2$ (product codes: A1296, C1013 and N1650, respectively, sigmaaldrich.com) to achieve the desired T1 and T2 combinations in the range of 50-3500 ms. Each preparation was heated in a 2L beaker on a standard hot-plate stirrer for at least one hour until the solution was completely clear. After topping up for the water lost during heating, the contents were quickly dispensed sequentially into individual tubes. Small amounts of gel were dispensed to the lid tops to decrease the volume occupied by air. After the tops adequately gelled, the lids were closed, assigned sequential numbers in the order of filling, and left to gel completely at room temperature. Tubes with differing properties and the same filling sequence number were stacked into a 10x10x14.5 cm^3 container (1L, 310 series, PVC container, cjk.co.uk) as a 3x3 array (**Figure S1b**). The outside was filled with un-calibrated agarose gel combinations, including two layers of stained gel intended to help localize the phantom center for scanning (**Figure S1c**). The lids were closed and protected with standard household silicone against

inadvertent opening. The containers were numbered with the sequential tube filling numbers, post-fixed by "/2013" to reflect the year of manufacture. An MR-safe thermometer strip (14-40°C Dual Scale LCD, 1 °C resolution, colourchanging.co.uk) was attached to the phantom body (**Figure S1c**). To assure better protection from damage and improve internal thermal uniformity, the phantoms were inserted into a tight-fitting custom-made card box (Style 0203, double wall flute, L150xW110xD110, ascdirect.co.uk, **Figure S1c** and **Figure S2a**). Side and bottom walls were folded to quadruple wall thickness for additional rigidity and thermal insulation. The phantom was secured internally with expanding foam and stickers. Signage was attached to the exterior of the box to guide standardized placement of the phantom and coil in the scanner **(Figure S2**). Two additional phantoms (here NiSO4 and NaCl doped water phantom) on either side are recommended to ensure adequate coil loading. All phantoms were individually batch scanned in randomized order within one month of manufacture in one session to confirm the consistency of the manufacture.

Section S2 HCMR QA protocol specification

The sites were provided with imaging manuals and HCMR QA protocols to perform five repeated ShMOLLI acquisitions, an inversion recovery spin echo (IR-SE) acquisition and a multi-echo SE acquisition with the following specifications.

1) Repeated ShMOLLI T1 sequences: echo time (TE) = 1.07ms; repetition time (TR) = 3.57ms; inversion times (TI) = 100, 1100, 2100, 3100, 4100, 180, 260ms; flip angle (FA) 35°; FOV = 270x360mm^2; matrix size 384x288; slice thickness 8mm; anterior and posterior surface coils; GRAPPA x2. A waiting time of 15 seconds between measurements was advised.
2) Slice-selective IR with a turbo spin-echo readout with turbo factor 7 (turbo factor 2 acquired, not used); to provide reference T1 relaxation time: TE = 11ms; TR = 10000ms; TI = 33, 100, 300, 900, 2700 and 5000ms; FOV = 360x360mm^2; matrix size = 256x256; slice thickness 8mm.
3) Multi-echo SE sequence to provide reference T2 relaxation time: TE = 15 - 480ms every 15ms; TR = 9000ms (TR = 2000ms acquired, not used); FOV = 360x360mm^2; matrix size 256x256; slice thickness 8mm.

The overview of QA scanning steps is given in **Figure S3**.

Section S3: ShMOLLI T1 predication model

The quality assurance models predicting the ShMOLLI-T1 ($\widehat{\mathrm{T1sh}}$) from reference measurements were established as (**Figure S6**):

$$\widehat{T1sh} = \begin{cases} T1ref(-2.68 * (T2)^{-0.76} + 1.024 + Res(T1ref)) & at\ 1.5T \\ T1ref(-5.50 * (T2)^{-0.94} + 1.005 + Res(T1ref)) & at\ 3T \end{cases},$$

where the residual correction is common between 1.5 and 3T (**Figure S7**):

$$Res(T1ref) = -8.21e\text{-}12 * T1ref^3 + 4.44e\text{-}8 * T1ref^2 - 6.78e\text{-}5 * T1ref + 2.75e\text{-}2.$$

Section S4: Additional experiment on T1 underestimation and inadequate Mz relaxation

To verify the source of low T1sh observed in individual acquisitions in 24 QA scans, we hypothesized that insufficient waiting time after scanner adjustments caused the T1 underestimation, because the longitudinal magnetization (Mz) had not recovered to baseline when the acquisition began. The two most likely factors affecting Mz are shimming and frequency preparations. To test this hypothesis, we devised an experiment to reproduce the T1 underestimation observed during the QA. The effect of insufficient waiting times after frequency adjustments is shown in **Figure S8a**. Impact of shimming appears to follow a similar trend (**Figure S8b**). The results demonstrate that the underestimation of T1 can reach sizeable levels with insufficient waiting times, affecting the long T1 compartments the most. All T1 values returned to within QA tolerance after approximately 10 seconds.

We confirmed that insufficient waiting time after a positioning scan or shimming caused an underestimation in T1sh values. This additional data allow to reduce the previous recommendation of 15 seconds of waiting time in HCMR protocols to a new recommended waiting time of a minimum of 10 seconds after an Mz manipulation, such as adjustment for frequency, phase, and shimming. Operator training and adherence to the protocol are essential not just to correctly deploy the T1 method, but especially important for in-vivo T1-mapping for clinical use, where underestimation of T1 may lead to an incorrect diagnosis.

Table S1: List of sites providing the QA scans.

HCMR site label	Site information	Manufacturer	Model Name	B0 (Tesla)	Number of scans
1	Virginia, United States	SIEMENS	Avanto	1.5	1
2	Cleveland, United States	Philips	Achieva	1.5	1
3	Brigham and Women's Hospital, United States	SIEMENS	Trio	3	2
5	Johns Hopkins Hospital, United States	SIEMENS	Avanto	1.5	2
11	Houston Methodist, United States	SIEMENS	Avanto	1.5	3
			Skyra^{fit}	3	1
			Verio	3	1
13	St. Luke, United States	SIEMENS	Avanto	1.5	1
14	Duke Cardiovascular MR Center, United States	SIEMENS	Avanto	1.5	5
			Verio	3	6
16	Yale School of Medicine, United States	SIEMENS	Aera	1.5	1
17	Northwestern University, United States	SIEMENS	Aera	1.5	3
18	Montreal Heart Institute, Canada	SIEMENS	Skyra	3	2
19	University of Calgary, Canada	SIEMENS	Skyra	3	3
22	University of Leicester, United Kingdom	SIEMENS	Aera	1.5	3
23	London Chest Hospital, United Kingdom	SIEMENS	Aera	1.5	9
24	Kings College St. Thomas, United Kingdom	Philips	Achieva	3	1
			Ingenia	1.5	1
	Kings College London, United Kingdom	SIEMENS	Aera	1.5	1
25	University of Edinburgh, United Kingdom	SIEMENS	Verio	3	3
26	University of Leeds, United Kingdom	Philips	Achieva	3	2
			Ingenia	1.5	2
27	London Royal Brampton Hospital, United Kingdom	SIEMENS	Avanto	1.5	3
			Avanto fit	1.5	2
28	University of Glasgow, United Kingdom	SIEMENS	Verio	3	1
29	University of Aberdeen, United Kingdom	Philips	Achieva	3	2
31	University of Heidelberg, Germany	Philips	Achieva	1.5	1
			Ingenia CX	1.5	1
32	Berlin Experimental Clinical Research Center, Germany	SIEMENS	Avanto^{fit}	1.5	1
			Verio	3	1
33	Stuttgart, Germany	SIEMENS	Aera	1.5	1
34	University of Rome, Italy	SIEMENS	Avanto	1.5	2
36	University Vita Salute San Raffaele, Italy	SIEMENS	Aera	1.5	2
37	Florence, Italy	SIEMENS	Aera	1.5	5
39	Erasmus, Netherlands	GE	Discovery	1.5	1
40	Amsterdam, Netherlands	SIEMENS	Avanto	1.5	2
41	St George's University of London, United Kingdom	Philips	Achieva	3	4
43	Oregon Health and Science University, United States	SIEMENS	Trio	3	2
46	University of Southampton, United Kingdom	SIEMENS	Avanto	1.5	1
47	Beth Israel, United States	SIEMENS	Aera	1.5	1
48	NYU Mount Sinai, United States	SIEMENS	Avanto	1.5	2
49	University of Bristol, United Kingdom	SIEMENS	Avanto	1.5	3
50	McGill, Canada	SIEMENS	Skyra	3	2

Figure S1. HCMR phantom design. (a) A single phantom compartment filled with gel; (b) Nine phantom compartments arranged as a 3x3 array within a container; (c) The phantom with a thermometer attached is encased safely in a cardboard box. The packaging provides protection, stability and thermal insulation to slow down drifts and to limit temperature gradients within the phantom.

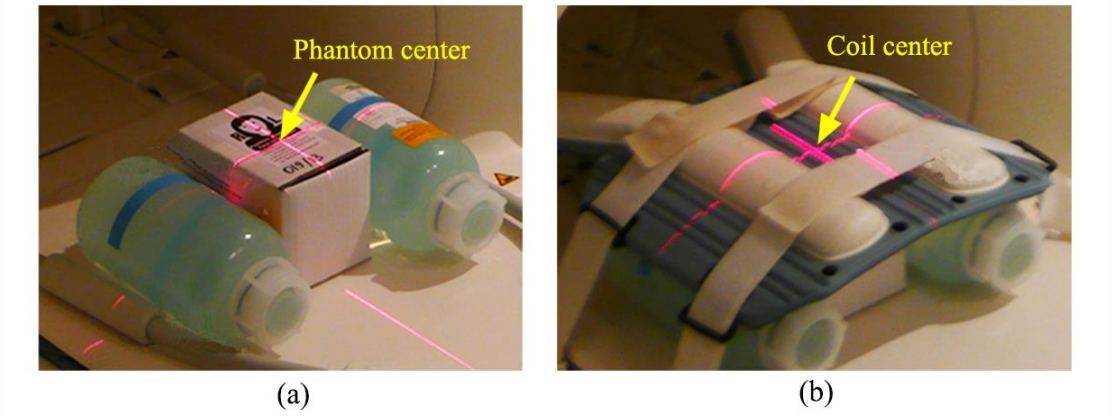

Figure S2. Phantom positioning for HCMR quality assurance scanning. (a) External appearance of the HCMR phantom designed to assure the correct orientation and positioning. (b) Anterior coil placement.

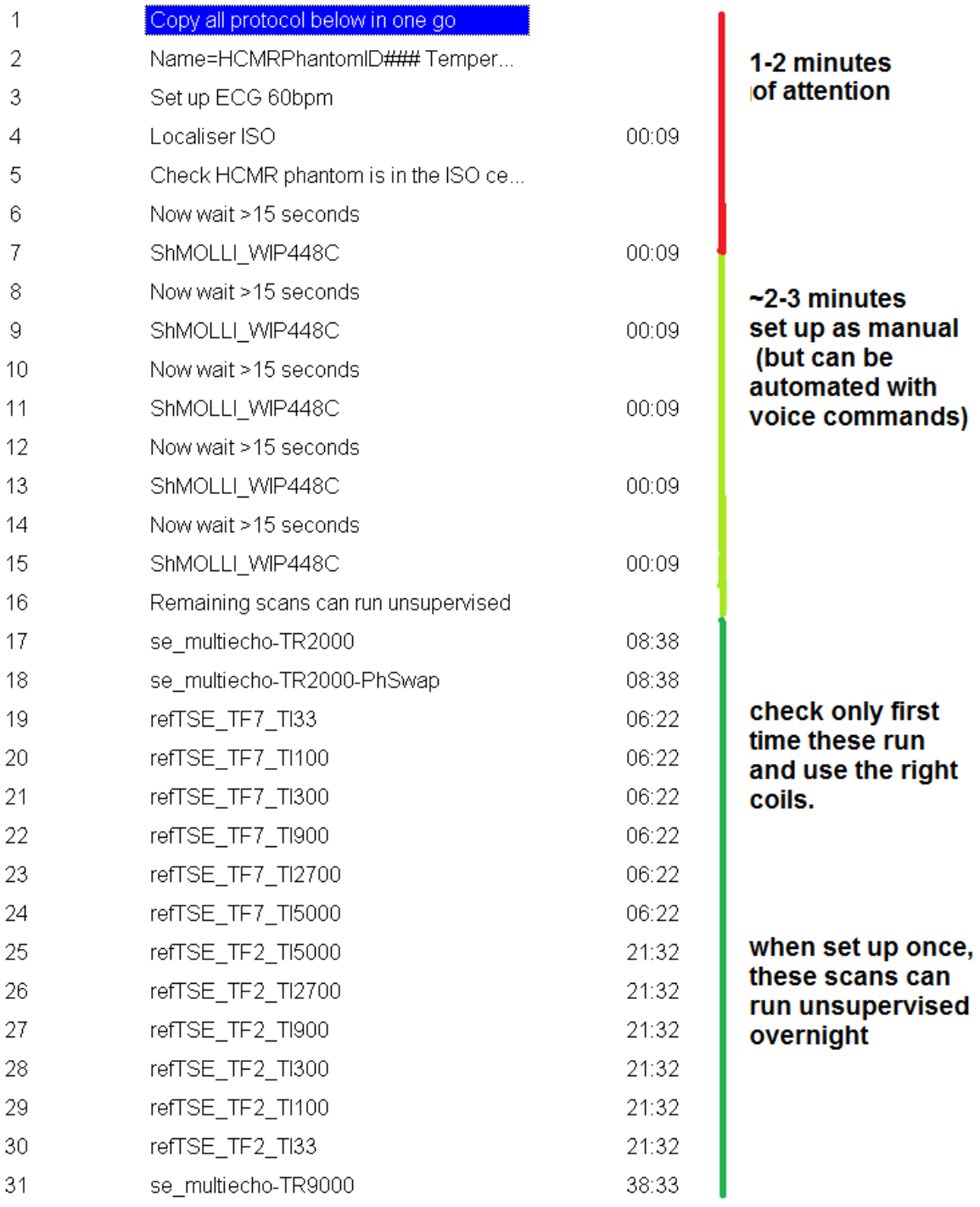

Figure S3. HCMR QA scanning steps. Note that the default QA protocol requires manual wait between ShMOLLI T1 maps. The pauses can be replaced with adequately long (>15 seconds) automated breathing instructions.

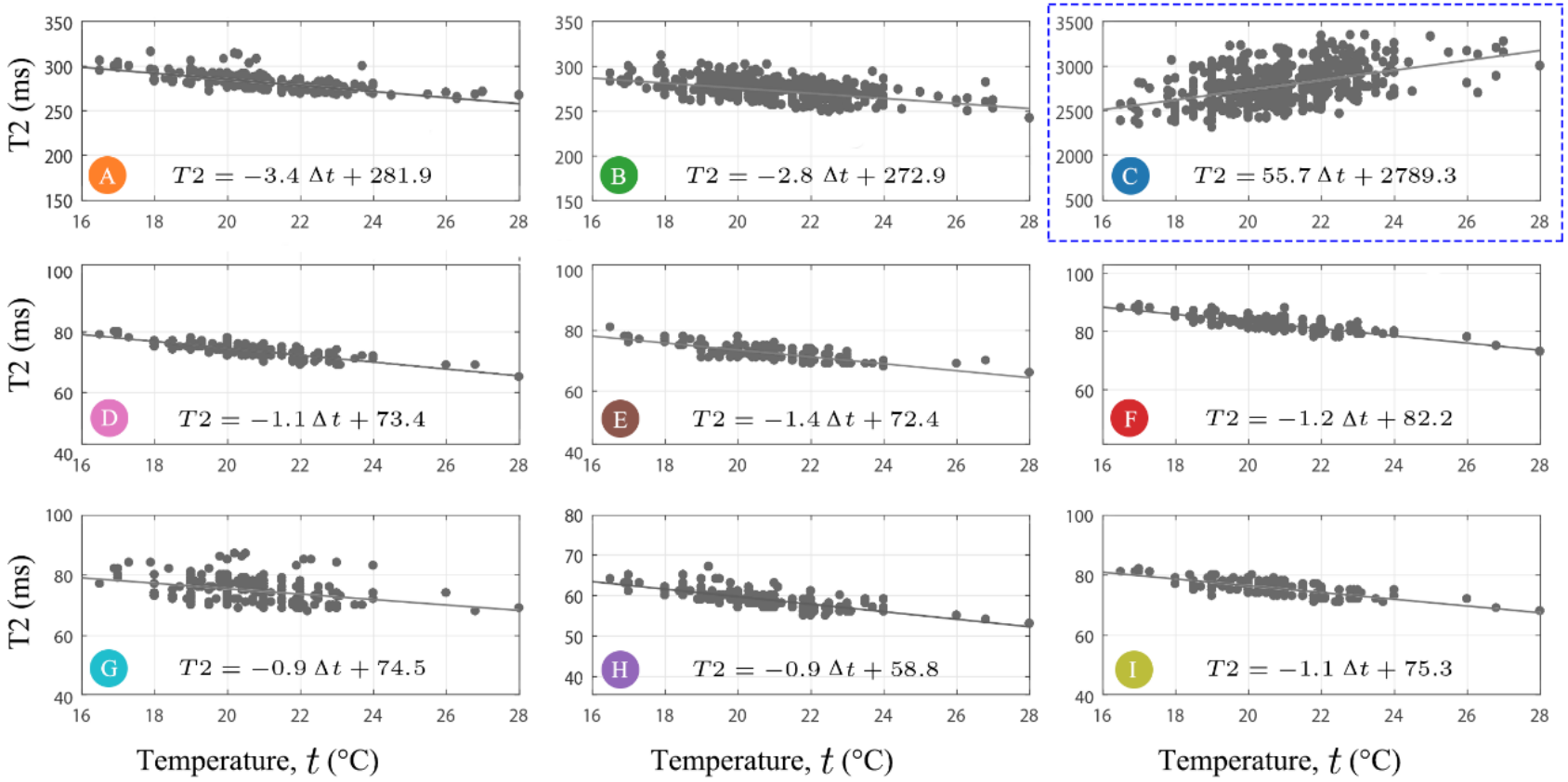

Figure S4. Temperature sensitivity of T2 (ΔT2/Δt, ms/°C) in the Oxford core lab dataset pooled between 1.5T and 3T. In the linear regression equations, 'Δt' is the phantom temperature minus 21°C. T2 showed a linear negative dependency on temperature for all the gel phantom compartments; water compartment #C sensitivity was positive at 55.7 ms/°C (outlined in blue).

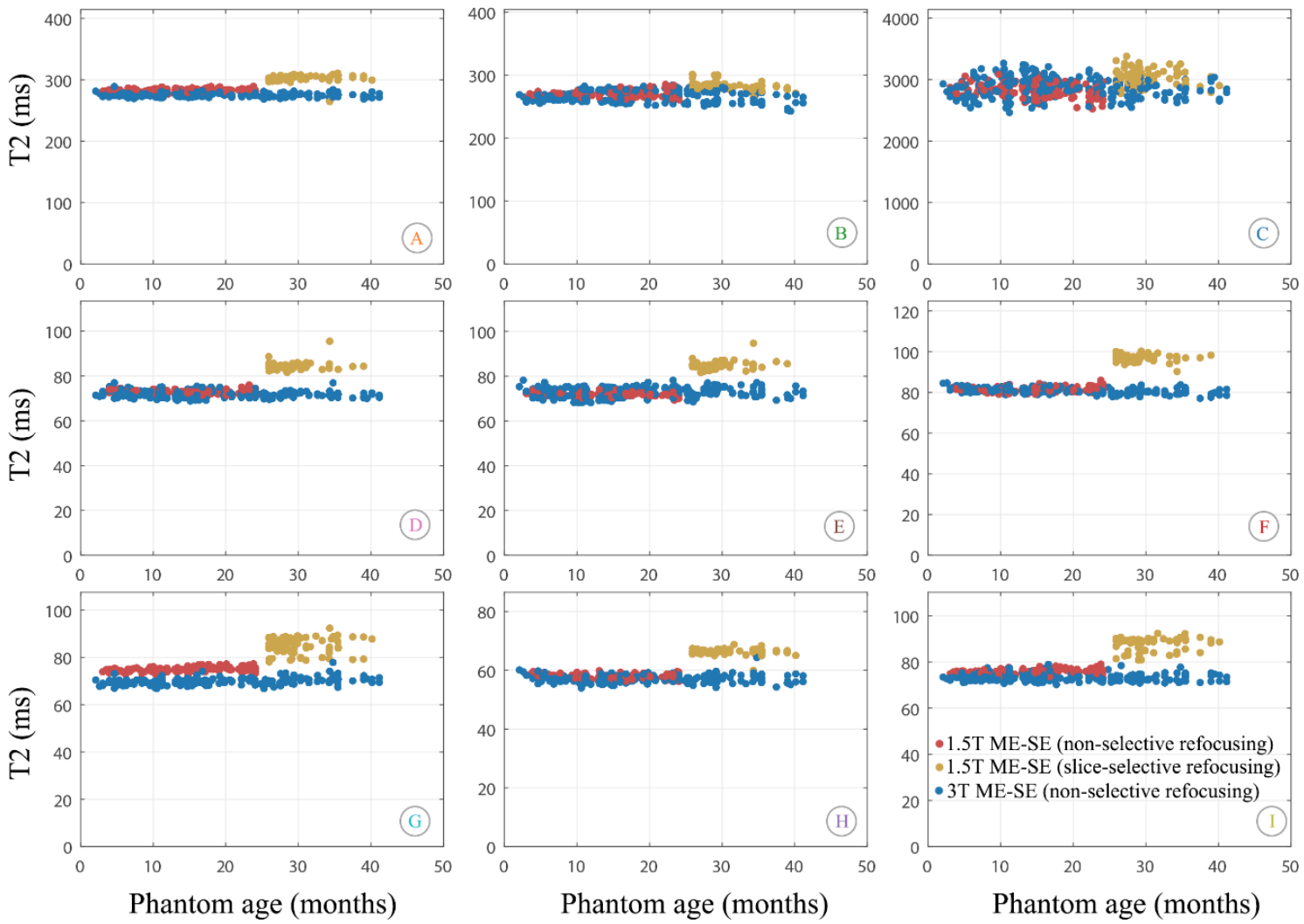

Figure S5. T2 of 4 phantoms over a period of 40 months at 1.5 T (red and yellow) and 3T (blue). This showed no significant T2 drift over time. A shift in measurements of T2 at 1.5 T is due to a change from multi-echo spin-echo sequence with non-selective refocusing pulses to one with slice-selective refocusing pulses.

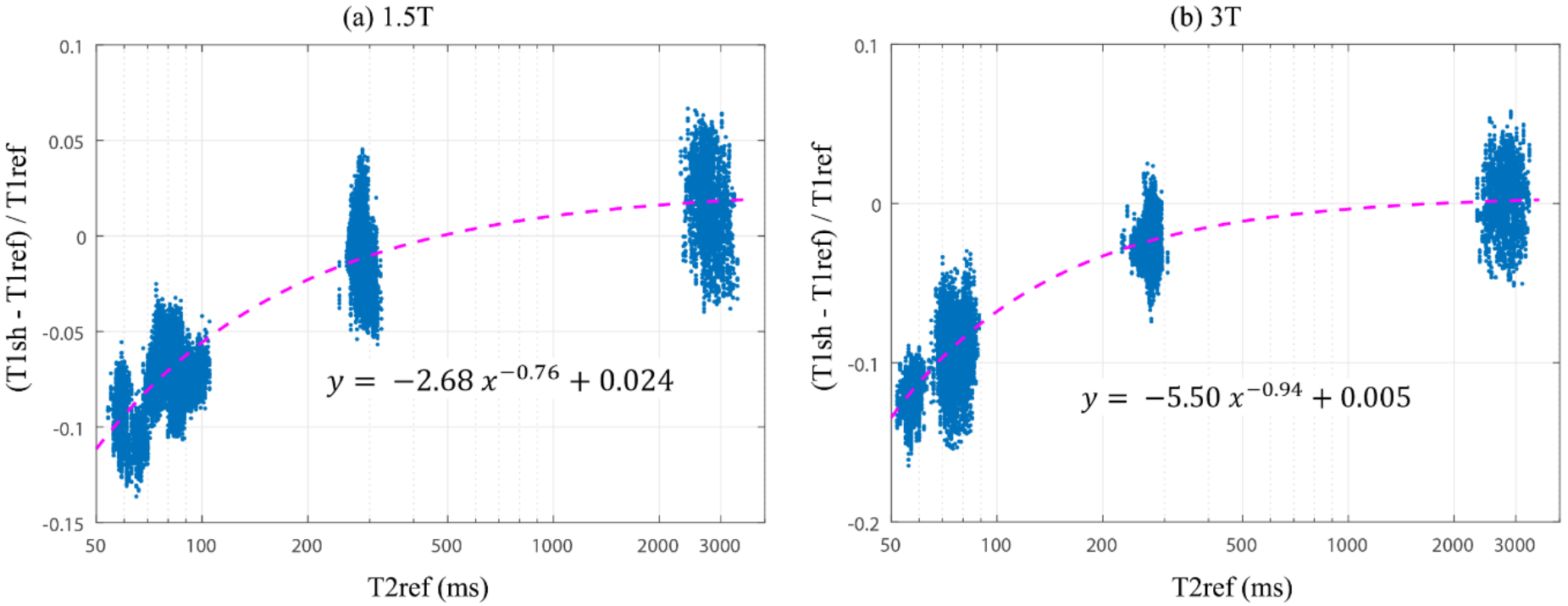

Figure S6. T2 dependency of the relative underestimation of ShMOLLI T1 (T1sh) from reference T1 (T1ref) at (a) 1.5T and (b) 3T. X-axes are shown in log scale. An empirical model (dashed line) is fitted to the dataset, with the corresponding coefficients calculated for 1.5T and 3T data samples.

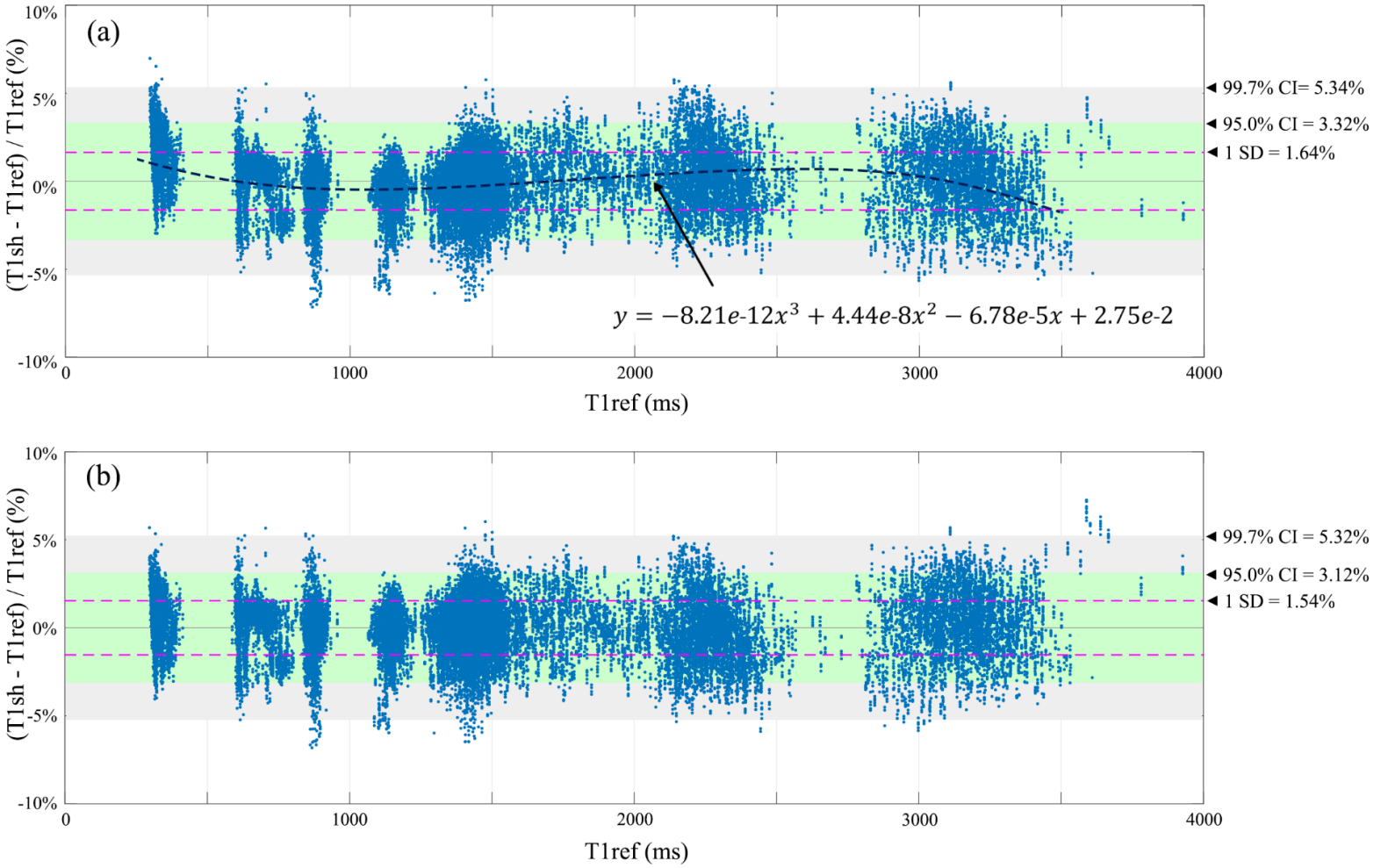

Figure S7. Residual errors and confidence range of the ShMOLLI T1 (T1sh) prediction model. X-axes are reference T1 (T1ref). Shown here are the 1 SD range (magenta dashed lines), 95% confidence interval (CI) (green range) and 99.7% CI (gray range). (a) Residual error assuming T2 as the predominant driving factor of measurement errors in ShMOLLI T1, with the effect corrected using T2 dependency models established in **Figure S6**. This significantly reduced the root-mean-square differences between ShMOLLI T1 and reference T1 from 7.24% to 1.64% (p-value <0.001). (b) Residual error after the perceivable small trend in (a) was compensated for using a third order polynomial (blacked dashed line in top panel). This further reduced the residual error to 1.54%, achieving a unity correlation between ShMOLLI T1 and reference methods (R^2=99.9%). Note: Residual errors are pooled together for 1.5 and 3T.

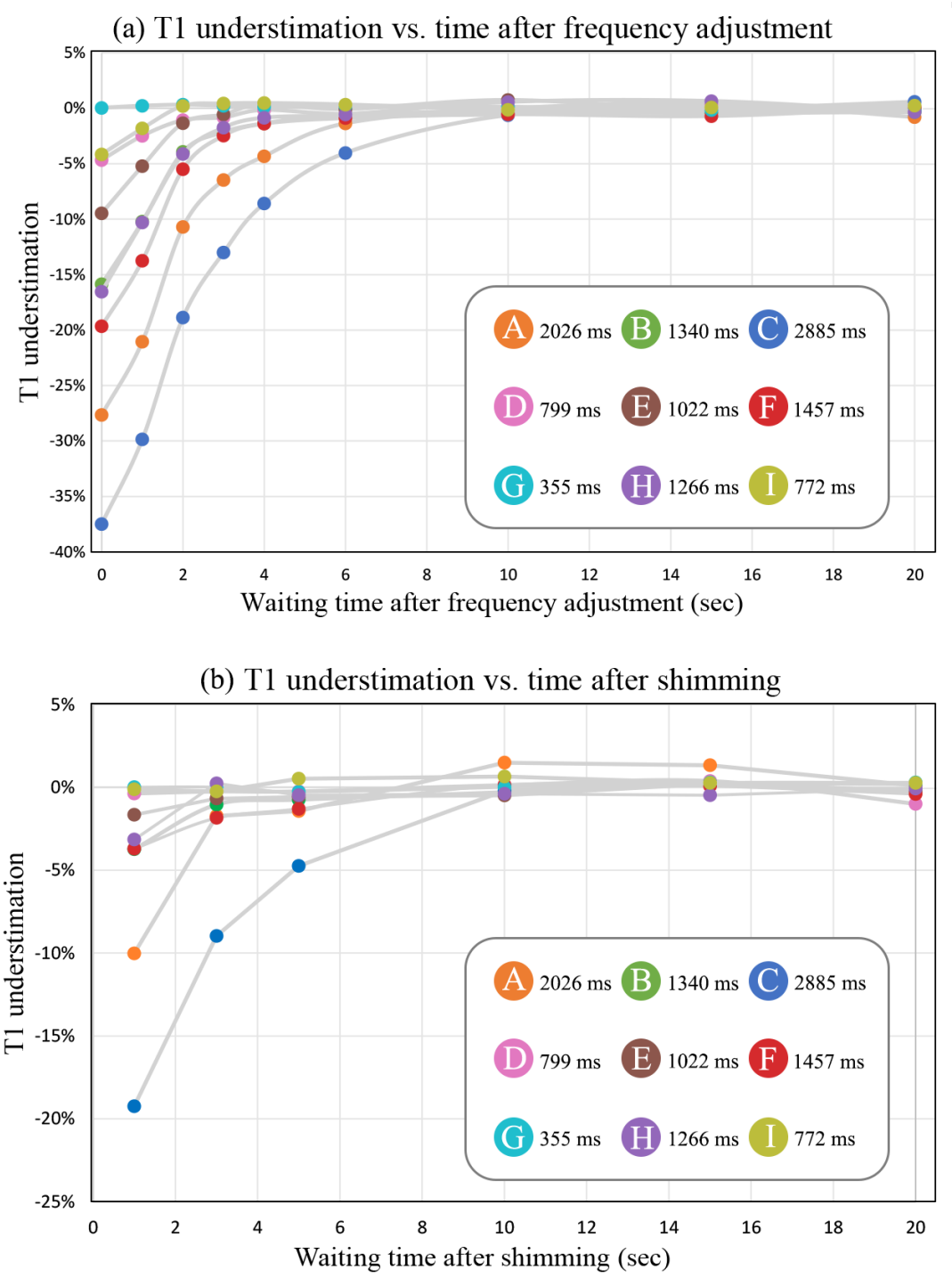

Figure S8. Underestimation in apparent T1 values due to incomplete recovery of baseline Mz as a result of inadequate waiting time from preceding (a) frequency adjustments, or (b) shimming. Shown are ShMOLLI T1 measurements at 1.5T. Baseline T1 values (ms) of each phantom compartment are given in the legend. Y-axes are the relative departure from optimal T1 values with adequate waiting time, as stated in the legend.