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1 **Agreement between Sensors and Peripheral Temperature**

2 **Measurements in Febrile Patients**

3 **Running Title: Temperature sensors and febrile patients**

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1 **Introduction**

2 Measuring human body temperature has been recognised as a major clinical sign for more than
3 150 years. Body temperature influences clinical management decisions and the diagnosis of
4 certain diseases, but is also an important indicator for estimating body metabolism, body
5 movement and physical activity [1,2].

6 When an infectious disease occurs, fever is one of many important indicators; the febrile
7 response means that the body is fighting the infection [3]. It is referred to as a “fever” when the
8 core temperature (head and thorax) is above 38.3°C [4]. The normal core temperature range is
9 between 36.5 °C and 37.3 °C; the periphery is 2 to 4 °C lower than that of the core [2].

10 There are several non-vascular methods to assess core temperature, including oesophageal and
11 urinary bladder measurements [5]. However, these non-vascular methods are invasive because
12 they require the use of a catheter and measuring rectal temperature creates a sense of
13 humiliation and discomfort. On the other hand, peripheral temperature measurements, such as
14 axillary temperature, tympanic temperature and temporal temperature are non-invasive but
15 may underestimate the core temperature and increase contact transmissions [6]. Peripheral
16 temperature measurements could be influenced by the following reasons: patient activity, basal
17 metabolism rate, fat mass, skin blood flow, measurement errors (incorrect thermometer
18 positioning) and ambient temperature.

19 Non-contact methods are particularly valued in highly contaminated environments. The ideal
20 measurement method must be accurate, precise and non-invasive; in addition, the ideal site for
21 measurements must meet the following requirements: not be influenced by ambient
22 temperature; reflect the core temperature quantitatively and quickly; and be as non-invasive as
23 possible [7].

24 In clinical practice, axillary thermometers, tympanic and temporal infrared thermometers are
25 used frequently. However, a recent meta-analysis showed that measurements taken by
26 peripheral thermometers were highly variable. This analysis included 75 studies, involving
27 8,682 patients from 21 countries. This analysis concluded that most peripheral thermometers
28 were not accurate enough to be considered as clinically acceptable core temperature
29 measurements [8].

30 Ingestible telemetric body core temperature sensors have been extensively used in sports
31 medicine specially to track core temperature during exercises. These non-invasive temperature
32 measurement methods have been established as valid index of core temperature in several
33 studies and have been suggested some time ago as having a good potential for ambulatory
34 monitoring [9,10]. A recent study compared four different models of ingestible capsules and
35 demonstrated the excellent consistency and accuracy of this device [11]. In clinical medicine
36 and, specifically, in infectious diseases, measuring the temperature of bedridden patients is
37 essential, yet takes nursing time and disturbs patients during the night. While ingestible
38 telemetric body core temperature sensors have been shown to correlate with rectal temperature
39 [12], they have not yet been compared to routine temperature measurements in clinical care in
40 patients with fever.

41 This study assessed the agreement between peripheral temperature measurements used in
42 clinical practice (axillary, non-contact) and both skin temperature recorded by skin sensor and
43 core temperature measurements taken by an ingestible capsule in a single cohort of febrile
44 patients.

45

46

47 **Materials and methods**

48 **Study design**

49 This open-label study was conducted in the department of infectious diseases at the University
50 Hospital Institute Méditerranée-Infection located in Marseille, France. All the procedures for
51 this study were approved by the Ethics Committee of Sud-Méditerranée IV (N° 180204) and
52 the study was registered on the French register for clinical trial (ANSM) under N° ID-RCB:
53 2018-A0014748 and in the European clinical trials database EudraCT under number **2018-**
54 **004812-23**. In accordance with medical research ethics, all participating patients are protected
55 (in accordance with the principles that originate in the Declaration of Helsinki). Each eligible
56 patient was included in the study after providing their written informed consent. Patients were
57 informed by the investigator or co-investigator of the study to the extent possible, based on
58 their understanding.

59 To measure axillary temperature, this study used a mercury-free thermometer (Geratherm®
60 Classic medical thermometer, CE0197, certified by NF EN ISO 13485); a new sensor, the
61 eTact® (BodyCap®, Caen, France) was used for skin temperature. An infrared thermometer
62 was used for non-contact forehead measurement in this study (HYLOGY Non-contact Infrared
63 Thermometer, Model: MD-H26, CE0123, US FDA approved).

64 An ingestible sensor (e-Celsius performance pill ®, BodyCap®, Caen, France) was used for
65 core temperature measurement. This ingestible capsule is a class IIB medical device and holds
66 certification ISO13 485 and the CE mark, providing continuous measurement of
67 gastrointestinal temperature (more detail, see Supplementary Appendix User Guide e-
68 CELSIUS Performance). All calibrations of the devices were performed by the manufacturer
69 in the 2018 version [12].

70 **Subjects**

71 This study included all patients who presented fever upon admission. Most were patients
72 with acute infectious diseases: pneumonia, urinary tract infections, soft tissue infections, and
73 all types of fever could be included in this study. All participants were social security insurance
74 beneficiaries aged 18 years or older.

75 The exclusion criteria included: 1) pregnant or lactating women, 2) patients with or presenting
76 a risk of intestinal disorders that can lead to obstruction of the digestive tract, including
77 diverticulitis, 3) patients with motility disorders of the gastrointestinal tract, 4) patients who
78 had undergone surgical procedures in the gastrointestinal tract, 5) patients with known
79 swallowing disorders, 6) patients who had to undergo MRI scans (and who should thus avoid
80 strong electromagnetic fields during the period of use of the system), 7) patients weighing less
81 than 40 kg and vulnerable persons.

82 **Study protocol**

83 During the study, we collected each the pathologies, demography, medical history and
84 medications of each patient using a bedside recording system developed in the institute (Florea
85 O, Boudjema S, Magnin C, Brouqui P, Dufour JC, manuscript in preparation).

86 For every patient participating in this study, temperatures were recorded over a 48-hour
87 observation period with axillary and non-contact forehead temperature measured by a mercury-
88 free thermometer and infrared thermometer every two hours (8.30am, 10.30am, 12.30pm,
89 2.30pm, 4.30pm); skin temperature was measured by eTact patch every minute. The core
90 temperature was measured by the ingestible capsule (BodyCap©) every five minutes.

91 Axillary temperature measurements were taken from the patient's left arm and environment
92 temperature was kept at 25 °C (to minimise the influence of environment) and non-contact

93 forehead temperature measurements were measured 5cm in front of the central forehead. Both
94 temperature measurements were recorded in the patient's case report, which was approved by
95 the Independent Ethics Committee. The ingestible capsule and eTact temperature
96 measurements were stored in the e-Viewer Performance monitor and eTact monitor, then
97 transferred to a computer in Excel format and all data were analysed by SPSS21 and R 3.4.2
98 (for Bland-Altman plot).

99 **Statistical analysis**

100 The primary objective was to assess the agreement and Intraclass Correlation Coefficients
101 (ICC) between the different types of body temperature measurement devices: ingestible
102 capsule, axillary, non-contact forehead and eTact (skin) temperature. The sample size
103 requirement for assessing ICC is 22 subjects (with power = 80%; alpha = 0.05; p=0.4; three
104 observations per subject and R_0 was set at zero). The normality of distribution was assessed by
105 analysis of Skewness and Kurtosis.

106 This study analysed the correlation coefficient (r) between axillary temperature measurements
107 and other temperature measurement devices. However, the assessment of the relationship
108 between the two methods is insufficient to demonstrate the degree of agreement and their
109 difference [13]. Consequently, to evaluate whether both methods give identical readings,
110 assessing the agreement (concordance) between series of repeated quantitative variables, it is
111 necessary to analyse the ICC. To calculate ICC, McGraw and Wong defined 10 forms of ICC
112 based on three "models" (one-way random effects, two-way random effects, or two-way fixed
113 effects) and two "types" (single rater/measurement or the mean of k raters/measurements). This
114 study chose the two-way mixed-effects model because repeated measurements cannot be
115 considered to be randomised samples. To complete the agreement analysis, the Bland-Altman
116 plot was used to assess the mean difference and construct the limits of agreement [14,15].

117 **Results**

118 The inclusion period ran from April 2018 to June 2018, during which 77 febrile patients were
119 admitted and hospitalised. A total of 26 patients were deemed eligible and participated in this
120 study.

121 Failure to obtain informed consent was the major cause of exclusion (20.78%, n=16), eight
122 eligible patients were not communicative, one was under guardianship, one was not conscious
123 enough and six eligible patients refused to participate. The second most common cause for
124 exclusion was the hypothetical requirement of MRI scans (15.58%, n=12). The third cause for
125 exclusion was swallowing disorders (12.99%, n=10) and other disorders (12.99%, n=10). The
126 last cause for exclusion was digestive system disorders (3.9%, n=3).

127 Table 1 reports the characteristics of the 26 patients: 12 females and 14 males, aged 48.6 ± 17.5
128 years old (mean \pm SD); their mean body weight was $65.9 (\pm 13.66)$ kg and blood pressure was
129 $118.6 (\pm 17.87) / 64.3 (\pm 12.98)$ mm Hg. The mean capsule transit time (during 48 hours of
130 observation) was $37.3 (\pm 14.8)$ hours. The shortest duration was four hours (one patient).

131 Following the collection body temperature measurements from four different devices over the
132 48-hour observation period, Table 2 summarises the percentages of missing measurements,
133 mean temperature, standard deviation, and maximum and minimum variable.

134 There is a 16.5% gap in temperature measurements for ingestible capsules. The main cause of
135 these missing measurements was the evacuation of the capsule before the 48-hour observation
136 period or a synchronisation problem between the monitor and the capsule (n=42, 11 patients).
137 eTact patches had fewer missing measurements at only 11.8% due to battery shutdown (n=18,
138 5 patients) or removal of the device by the patient (n=12, 2 patients). As for axillary and non-
139 contact measurements, there was a missing measurement rate of 16.5% (n=42) and 15.3%

140 (n=39) respectively, due to the absence of the patients at the time of recording and during the
141 weekend.

142 To highlight the usefulness of the ingestible capsule temperature measurements, Figure 1A
143 indicates the time trend data of all measurements in one selected patient. Figure 1B indicates
144 the time trend data of one patient with hypothermia.

145 The regression line between the axillary temperature measurements (T_{axi}) and non-contact
146 forehead temperature measurements ($T_{\text{no-c}}$), ingestible capsule temperature measurements
147 (T_{cap}) as well as eTact temperature measurements (T_{etac}) are shown in Figures 2. The coefficient
148 (r) between T_{axi} vs. $T_{\text{no-c}}$ is 0.47 (95% IC: 0.36; 0.57, $R^2=0.22$, $p<0.001$) and coefficient (r) is
149 0.85 (95% IC: 0.81; 0.98, $R^2=0.72$, $p<0.001$) between T_{axi} vs. T_{cap} . The correlation between T_{axi}
150 vs. T_{etac} is coefficient (r) =0.42 (95% IC: 0.30; 0.52, $R^2=0.17$, $p<0.001$). The ICC between T_{axi}
151 vs. $T_{\text{no-c}}$ is 0.34 (95% IC: -0.18; 0.63); 0.87 (95% IC: 0.55; 0.94) between T_{axi} vs. T_{cap} ; and 0.12
152 (95% IC: -0.09; 0.37) between T_{axi} vs. T_{etac} . Table 3 summarises the comparison of each
153 correlation and agreement between the three different devices and the axillary temperature
154 measurements.

155 We also assessed the correlation at the time of each recording (10 recordings in 48 hours); no
156 statistically significant differences were found during the 48-hour observation period.

157 Finally, Table 4 summarises the details of the Bland-Altman plot. This table shows the mean
158 difference of two paired of measurements as well as their standard deviation and the limits of
159 agreement. The mean difference between T_{axi} vs. $T_{\text{no-c}}$ is -1.18°C with 95% limits of agreement
160 of -2.96°C to 0.58°C . The mean difference between T_{axi} vs. T_{cap} is 0.48°C with 95% limits of
161 agreement of -0.60°C to 1.56°C . The mean difference between T_{axi} vs T_{etac} is -4.23°C with 95%
162 limits of agreement of -7.22°C to -1.23°C . Figures 3 indicate the difference of two pairs of
163 measurements.

164 **Discussion**

165 While pulmonary arterial blood temperature is considered to be the gold standard for measuring
166 core temperature, this invasive method cannot be used in non-ICU febrile patients. Ingestible
167 telemetric body core temperature sensors have been shown to correlate with rectal
168 temperature[11,16]. Rectal temperature has widely been dismissed in clinical practice due to
169 its invasiveness and discomfort. Axillary temperature measurement is currently the non-
170 invasive measurement that reflects the best core temperature (axillary temperature plus 0.5°C)
171 and has been recommended as the standard for neonatal care [1,17].

172 Several studies have shown that non-contact (forehead or temporal artery) temperature
173 measurements are a reliable, comfortable and accurate option for measuring body temperature
174 and screening for fever in the paediatric population [18–20], and they have been widely used
175 in airports since the outbreak of severe acute respiratory syndrome (SARS) [21,22]. In 2004,
176 the U.S. Food and Drug Administration (US FDA) approved the use of this thermometer in
177 children [20]. However, some studies have shown this method is not clinically acceptable in
178 adults [23–26].

179 In this study, the non-contact forehead temperature measurements show a weak uphill linear
180 relationship ($r=0.42$) and poor strength of agreement ($ICC <0.40$) with axillary temperature
181 measurements. The Bland-Altman plot shows that more than 95% of points are within the limits
182 of agreement, but 95% of points show that the difference between the T_{axi} vs. T_{no-c} is lower than
183 zero. The mean difference between T_{axi} vs. T_{no-c} is -1.18 °C, which is higher than the clinically
184 acceptable range (± 0.5 °C). This method underestimates core temperature because non-contact
185 forehead temperature measurements could be influenced by blood flow under the skin, body
186 metabolic rate and the distance between the thermometer and forehead. Moreover, according
187 to the Bland-Altman plot, the difference between the two temperature measurements increases

188 as the temperature increases. Therefore, this method is neither sufficiently reliable nor
189 clinically acceptable for screening for fever in adult febrile patients.

190 Skin sensors (eTact patches) exhibit a weak uphill linear relationship ($r=0.42$) and a poor
191 strength of agreement ($ICC < 0.40$) with axillary temperature measurements. Skin temperature
192 can be influenced by many factors such as blood flow under the skin, the body's metabolic rate
193 and ambient temperature [27]. Thus, this method was less consistent than the core temperature
194 measurements (SD of eTact measurements was 1.84 and the SD of ingestible capsule
195 measurements was 1.01). The Bland-Altman plot shows that 95% of points were within the
196 limits of agreement, but many of the points were further from zero. The mean difference was -
197 4.23 °C, as the theory indicated; the skin temperature was 2 to 4 °C below the core temperature.
198 However, this method did not correlate well with the reference temperature, so it is not
199 acceptable for fever screening.

200 In our study, the ingestible capsule shows a strong uphill linear relationship ($r=0.85$) and an
201 excellent degree of agreement ($ICC > 0.77$) with the axillary temperature measurements.
202 According to the Bland-Altman plot, 95% of points are within the limits of agreement, and the
203 mean difference between T_{axi} vs T_{cap} is 0.48 °C, which is within the clinically acceptable range
204 (± 0.5 °C). This difference between axillary temperature measurements and temperature
205 measurements of ingestible capsules is, as the theory indicates, in the range of 0.5 to 1°C.
206 Compared to other core temperature measurement methods, the ingestible capsule is less
207 invasive and more comfortable method for patients. This method produces continuous body
208 temperature measurements during gastro-intestinal transit. However, cold or hot food and drink
209 intake can influence capsule temperature measurements[28]. According to Domitrovich *et al.*
210 (2010), measurements of ingestible capsules are reliable after only 40 minutes of ingestion
211 (when the sensor passes the stomach) [29]. In our study, we therefore took this constraint into
212 account when analysing the data. Ingestible temperature sensors are an easy way to follow and

213 monitor core temperature; it has been reported that continuous core temperature measurements
214 help to predict the early diagnosis of hospital-acquired sepsis [30]. Continuous core
215 temperature measurements could offer a different perspective on patterns of fever and detect
216 abnormal core temperature curves at an earlier stage. Monitoring core body temperature in real
217 time on a continuous basis might be very useful in cases of factitious fevers, chronic infections
218 and fevers of unknown origin. Non aggressive, continuous real time recording of the body
219 temperature during infection offers a new tool to study the relationship between temperature
220 and the infectious process [31]. However, ingestible telemetric body core temperature sensors
221 have some limitations: the main one being the gastrointestinal transit time, as transit time varies
222 for each individual due to age, gender, diet and pathology. The variability of the transit time
223 ranges from 0.52 day to 5.6 days and the mean transit time is 2 ± 1.5 days [32]. This resulted
224 in missing measurements in our study, due to the absence of indications from the capsule.
225 However, if needed, capsules can be prescribed every three days and the monitor can follow
226 four capsules at the same time. Another inconvenience was the exclusion of patients who might
227 require an MRI scan, who represented 15% of febrile patients in our cohort. However, one final
228 positive aspect of this type of measurement is that, in our experience, the time spent by the
229 nurse waiting for axillary temperature readings was calculated in our study as 2.83 ± 0.66
230 minutes. The cumulated time spent by nurses waiting to collect axillary temperature readings
231 in our study was estimated at 12.26 hours. Although a full medico-economic study is required,
232 it is likely that the capsule would save time.

233

234 **Conclusions**

235 Of existing temperature measurement sensors, only the ingestible capsule has a good
236 correlation and agreement with axillary temperature measurement. It is sufficiently reliable to
237 adequately estimate the body temperature in clinical care. In addition, the capsules offer real-
238 time measurement (every 30 seconds, one minute, two minutes or five minutes). The number
239 of collection points, its non-invasiveness, and the remote control in real time offer new
240 opportunity for future investigation of fevers during the course of infectious diseases.

241

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247 Urkund®.

248

249 **Footnotes**

250 **Contributors**

251 Conceived and designed the experiments: PB, FH, CM. Performed the experiments: FH.

252 Analysed the data: FH, CM. Wrote the paper: FH, PB.

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257 **Conflict of Interest**

258 All authors are no reported conflicts of interest. All authors have submitted the ICMJE Form

259 for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to

260 the content of the manuscript have been disclosed.

261

262

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- 344

1 **Figure legends**

2 **Figure 1. Time trend data**

3 **A**, Time trend data of all measurements in one selected patient with acute community acquired
4 pneumonia. Black squares represent axillary temperature measurements; red points represent
5 ingestible capsule temperature measurements; green stars represent non-contact temperature
6 measurements; blue points represent eTact temperature measurements. **B**, Time trend data of a
7 patient with hypothermia.

8 **Figure 2. Regression line between the axillary temperature measurements (T_{axi}) and non-**
9 **contact forehead temperature measurements (T_{no-c}), ingestible capsule temperature**
10 **measurements (T_{cap}) as well as eTact temperature measurements (T_{etac}). With 95%**
11 **confidence interval.**

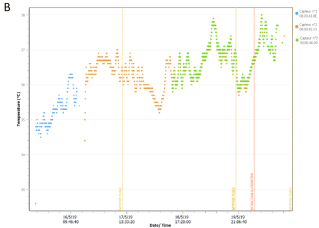
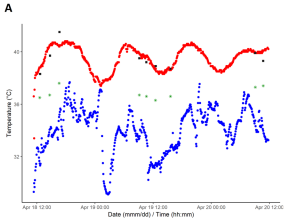
12 **A**, Regression line between the T_{axi} and T_{no-c} ($r=0.47$, $p<0.001$). **B**, Regression line between
13 the T_{axi} and T_{cap} . ($r=0.85$, $p<0.001$). **C**, Regression line between the T_{axi} and T_{etac} ($r=0.42$,
14 $p<0.001$).

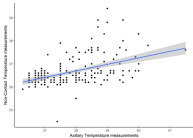
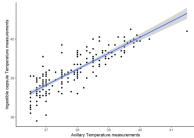
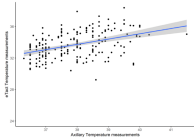
15 **Figure 3. Bland-Altman plot. Comparison of the difference between two measurements**
16 **with the 95% limits of agreement. The red line represents the mean difference between**
17 **two measurements, with 95% confidence interval (two grey dashed lines). Blue lines**
18 **represent the upper and lower limits of agreement and grey dashed lines represent their**
19 **95% confidence interval.**

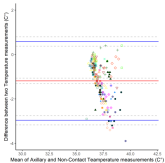
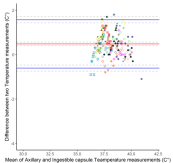
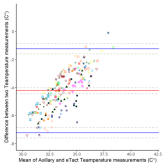
20 **A**, Comparison of the difference between the T_{axi} and T_{no-c} . The mean difference between
21 T_{axi} vs. T_{no-c} (-1.18°C). The upper and lower limits of agreement (-2.96°C and 0.58°C). **B**,
22 Comparison of the difference between the T_{axi} and T_{cap} . The mean difference between T_{axi} vs.
23 T_{cap} (0.48°C). The upper and lower limits of agreement (-0.60°C and 1.56°C). **C**, Comparison

24 of the difference between the T_{axi} and T_{etac} . The mean difference between T_{axi} vs T_{etac} (-
25 4.23°C). The upper and lower limits of agreement (-7.22°C and -1.23°C).

26



A**B****C**

A**B****C****Patients**

- Patient 1 ○ Patient 18
- Patient 2 ○ Patient 16
- Patient 3 ○ Patient 17
- Patient 4 ○ Patient 18
- Patient 5 ○ Patient 19
- Patient 6 ○ Patient 20
- Patient 7 ○ Patient 21
- Patient 8 ○ Patient 22
- Patient 9 ○ Patient 23
- Patient 10 ○ Patient 23
- Patient 11 ○ Patient 24
- Patient 12 ○ Patient 25
- Patient 13 ○ Patient 26
- Patient 14

1 Tables

2 **Table 1. Characteristics of the 26 patients.** This table shows patient demography, medication
3 and medical history.

Sex	n	(%)
Female	12	(46.2)
Male	14	(53.8)
Baseline	mean	(SD)
Age (years)	48.6	(17.5)
Body weight (kg)	65.9	(13.66)
Blood pressure (mm Hg)		
Systolic pressure	118.6	(17.87)
Diastolic pressure	64.3	(12.98)
Pulse (bpm)	95.4	(15.5)
Body temperature during inclusion (°C)	38.73	(0.74)
Capsule transit time (hours)	37.3	(14.8)
Treatments	n	(%)
Antibiotics	19	(33.92)
Antipyretic	8	(14.28)
Antivirus	4	(7.14)
Antimalarial	1	(1.78)
Other	24	(42.85)
Medical history	n	(%)
Surgical	7	(19.44)
Cardiovascular	8	(22.22)
Metabolic disorders	6	(16.66)
Pulmonary	2	(5.55)

Urinary	2	(5.55)
Gastro-intestinal	3	(8.33)
Infectious	8	(22.22)

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6 **Table 2. Descriptive statistics of axillary temperature, non-contact temperature, ingestible**
7 **capsule temperature and eTact temperature measurements during 48-hour observation**
8 **period.**

	Total N (measurement points)	Valid N	Missing (n, %)	Mean (°C)	Standard Deviation	Max (°C)	Mini (°C)
Axillary temperature (T _{axi})	255	213	42 (16.5)	37.84	1.02	41.5	36.3
Non-contact forehead temperature (T _{no-c})	255	216	39 (15.3)	36.66	0.61	39.4	34.5
Ingestible capsule temperature (T _{cap})	255	213	42 (16.5)	38.26	1.01	40.5	35.7
eTact temperature (T _{tac})	255	225	30 (11.8)	33.59	1.84	38.37	24.03

9

10

11 **Table 3. Analyses of correlation (Pearson) and agreement (Intraclass Correlations) among**
 12 **three different devices and axillary temperature measurements.**

	Correlation coefficient				Agreement		
	Pearson(r)	95% CI	sig.	R ²	ICC	95% CI	sig.
Non-contact forehead (Tno-c)	0.47	0.36;0.57	p<0.001	0.22	0.3445	-0.18; 0.63	p<0.001
Ingestible capsule (Tcap)	0.85	0.81;0.98	p<0.001	0.72	0.8730	0.55; 0.94	p<0.001
eTact (Tetac)	0.42	0.30;0.52	p<0.001	0.17	0.1229	-0.09; 0.37	p<0.001

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14

15 **Table 4. Detail of Bland-Altman plot among three different devices and axillary**
 16 **temperature measurements.**

	Mean Difference (°C)	Standard Deviation	Std. Error Mean	95% Confidence Interval of the Difference (°C)		limits of agreement ($d \pm 1.96SD$) (°C)	
				Lower	Upper	Lower	Upper
				Tno-c vs. Taxi	-1.1892	0.9049	0.062
Tcap vs. Taxi	0.4804	0.5549	0.0409	0.3997	0.5611	-0.6071	1.5680
Tetac vs. Taxi	-4.2316	1.5285	0.1091	-4.4470	-4.0163	-7.2277	-1.2356

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